ANNALS of ALLERGY

Published by
The American College of Allergists

Volume 18 February, 1960 Number 2

EVALUATION OF THE EMOTIONAL FACTORS IN ECZEMA AND URTICARIA

Essential Goals for Diagnosis and Treatment

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WITH OUR increasing knowledge of the interplay between the emotions and bodily functions it becomes evident that the allergist must bring to each patient not only his knowledge of normal and disturbed physiology and immunity but also a knowledge of his patient's emotions and attitudes. He must appreciate in its broadest scope the significance of what the allergic constitution means both physically and psychologically.

The allergic constitution, in terms of today's knowledge, is genetically determined. It is the primary factor in all allergic diseases. It places its imprint on immunologic mechanisms as evidenced by the presence of abnormal antibodies (reagins). It places its imprint also on the hormonal and autonomic nervous mechanisms as evidenced by such characteristic and related syndromes as bronchial asthma, hay fever, eczema and urticaria. It stamps its imprint, too, on the allergic's emotional development as evidenced by the characteristic emotional responses which accompany the immunologic and physiologic deviations.

The integration of all these aspects of allergy so as to make a psychosomatic whole, capable of recognition and therefore more amenable to treatment, is well illustrated in the clinical syndrome known as infantile eczema or in the adult form as atopic dermatitis.

In atopic dermatitis, more often than not, the specific immunologic

Presented as part of a panel discussion on "Evaluation of the Emotional Factors in Eczema and Urticaria" before the Fifteenth Annual Meeting of The American College of Allergists at San Francisco, California, March 20, 1959.

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abnormality (reagin) identifying the allergic constitution is demonstrable. The characteristic history and physical aspects of the dermatologic pattern are similarly demonstrable. That a typical pattern of emotional responses to environmental pressures is also demonstrable has been shown by various investigators. The genesis and growth of this emotional pattern is summarized in the following commentary on the psychological aspects of the typical life-history of the allergic patient with atopic dermatitis.

In the same manner as other allergic individuals, the allergic individual with atopic dermatitis has been seen to be inordinately fearful of being abandoned by his mother or by some person whom he takes as a mother-substitute. This is a threat left over from the earliest days of life when oral feeding satisfactions and diffuse skin contacts with the mother were of primary importance to his sense of security, as these are with every infant. For real or imagined reasons, the patient with atopic dermatitis carries with him as he grows, unconscious feelings that skin contacts were either denied him, were insufficient or were unsatisfactory.

Originally, from his sense of being deprived, or as he felt it—unloved, he became excessively hungry for his mother and excessively angry at her. In his hunger, he wanted in fantasy to get more of her. He clutched at her with fists and nails. He went after breast or bottle as if he wanted to devour or incorporate it, as a part of mother, with clamping jaws and later with biting teeth. In his anger, he wanted in fantasy to hurt his mother. The clutching fists and nails, the clamping jaws and biting teeth put this, as it were, into action for him. In primitive fashion the nails became equated with the teeth as symbols of intake to satisfy hunger for love and as weapons for venting anger at one and the same time. But because his mother's body was not always available to him, and also because he feared her response to his attack, he acted out the anger on himself by scratching himself instead of his mother. This was dramatically demonstrated when a two-year-old girl, her whole body covered with eczema, stopped the incessant scratching of her own skin only when inadvertently permitted to scratch her mother. She would then furiously claw her mother. But as soon as the mother pushed her away, the child would immediately resume scratching herself.

Obviously, scratching the mother cannot be sanctioned. The patient with eczema ordinarily knows this. He comes to conclude therefore that any feelings which push him into even wanting to do such a thing are wrong. In consequence he represses his hunger-for-love and his anger at his mother. He turns to indirect attempts to resolve his tension. He seeks two major emotional goals: (1) To obtain more of whatever attention he can interpret as love; and (2) to release, in unrecognizable disguise, against himself, the anger he would like to vent against the mother. For both of these goals he uses his skin.

He has found perhaps from a previous, fortuitous skin eruption, whether

allergically induced or not, that this did bring from his mother attention that he could interpret as love. This attention came in the form of local applications, as rubbing with ointments or wrapping with compresses. Such manipulations brought some degree of satisfactions, moreover, to salve his need for body contact. But still this did not allay his anxiety because it left untouched his conflict between the hunger-for-love and the anger at his mother. Despite using his nails to hurt himself instead of his mother, he continued to fear his feelings and to dread also that they might perhaps be discovered. And so he kept them sealed in his unconscious mind. Thus covered, they accompanied him through the different psychological developmental stages of his growth. In each developmental stage they became associated with wishes and fantasies fitting in with the impulses and fantasies characteristic of that particular stage.

In earliest life, as already indicated, one of the two major satisfactions sought by the child comes through diffuse skin stimulation. Whereas other allergics give up this continuing focus and turn to a more mouth-involving, respiratory pattern, such as asthma or hay fever, the eczematous individual keeps to his skin.

This shows up graphically in diagnostic and psychotherapeutic play sessions with eczematous children. Here one sees repeatedly illustrated the continuing wish for skin satisfactions. One sees illustrated also the anger toward the mother and the turning of this anger back against the self. One sees nails and teeth being put together, or equated, in acts of scratching, clawing and biting.

Over and over again the children choose wild baby animal toys to play with. They make the babies devour and bite, pounce on and claw their mothers. And then the babies have to be bitten back, cut up, eaten and scratched out in turn. Over and over children with skin troubles show a concentration also on "being rubbed." They use finger paints as much by rubbing it on their hands as they do by manipulating it on paper. In their play with clay they frequently want to rub it all over themselves, sit in it, wash it off and rub some more on. This is recognizable as a method of getting skin satisfaction but it has its obverse side also, for it can also be an expression of anger used as a "smear" instead of a "rub."

This takes us into another stage of infant development, the stage where in our culture much emphasis is given to toilet training. The child is told to "do it for mother." He is wiped and washed. And so when he brings her an even bigger mess smeared over his whole body—that is, his skin eruption—he symbolically brings her a gift for which he hopes to be rewarded, by being rubbed, for instance, with medicinal stuffs. But he has also recognized that his mother finds "dirty" what she has asked for. And so, at one and the same time he can use it to vent hostility. He can turn it magically in his imaginings from something she wants to something she hates.

At still a later stage of development, children begin to focus on the genital area for tactile skin satisfaction. This is more frequently than not either openly or tacitly forbidden. And so, the child with eczema just as frequently uses his whole body instead of the genital area to receive the skin stimulation he desires. But because the struggle for satisfaction remains tied in with earlier hostility, he erupts with hostility and scratches instead of rubs.

In the older child or adult patient with atopic dermatitis, traces may remain of any of the emotional meanings from any or all stages of psychological development.

A woman in her late twenties brings illustration from the first stage when infantile demands for diffuse skin contacts failed and engendered anger. Her mother had not wanted her and had placed her in the home of an already overburdened great-aunt. Her one "sweet memory" out of childhood was of the rare moments when her great-uncle would sit in the kitchen and rock her. When she married, the thing she wanted most in her house was an old-fashioned rocking chair. When a friend on seeing it remarked that she was a bit foresighted in thinking of rocking her babies, she was astonished. A quick thought flashed into her mind, "That chair is only for rocking me and rocking me only!" In love-making she maneuvered things so that her husband would rock and stroke her. "That sort of petting is the best part of it all!" she declared. For a while all went as she wished it. But then, the husband revolted and her skin flared up violently. "I never *say* anything about it to him," she said, "But I get so mad I could flare up and burst!"

As illustration from the next stage of emotional development, the exudation and crusting appear often to represent the hostile smearing that became fixed when toilet habits were being pressed. One adolescent expressed this when he exclaimed, 'Everyone can see I'm a mess-up. My skin is cruddy, so the hell with them all!"

As for the third stage mentioned, the fantasy of the whole body as a genital organ is typified by a man of thirty who said, "My body feels like a big, itchy penis. I want to rub it gently to make it feel good but I always end up" (turning the hostility against himself) "by scratching instead."

In urticaria the same pattern of emotional underlay essentially holds. But the angry part is nearer the surface. It is more often pre-conscious rather than unconscious. Usually some specific psychological insult which may be chronically repeated, precipitates the appearance of hives.

Whether eczema or urticaria is manifest, the physiologic disturbances are still directed at securing tactile stimulation and at releasing anger turned back upon the patient's own skin surface. Unconsciously he still hopes that through his illness he will be fed the attention and the love that he seeks. And so he welcomes, as earlier, the application of medica-

tion to the skin by whomever he takes in his unconscious fantasies as "mother," whether it be marital partner, nurse or doctor. He may even fantasy himself as "mother" applying these medications to himself.

But because he still contains so much repressed anger he continues to erupt and tear at himself. At the same time he may indirectly and unsatisfactorily vent his anger on others in demanding behavior. He may exhibitionistically flaunt his skin as if he were saying, "There's nothing wrong with me!" In opposite fashion he may attempt by social and personal withdrawal to hide and cover, not only his skin but the self whom he condemns for unworthy wishes; or he may hide under actual physical coverings, ranging from long-sleeved shirts to dark glasses, trying unconsciously to keep from revealing what he has done to another through himself.

It is not necessary for the physician to be able to recognize and translate every symbolic psychosomatic expression. The important goals for him in treatment and therapy are to keep in mind the dual use to which the patient puts his symptoms and to try to help the patient in his whole orientation to find out more suitable and healthier ways of going after the two emotional ends at which he is aiming. Take the patient's second aim first—the need to express anger through his skin. The physician can encourage the patient to bring his anger out otherwise. He can, for instance, give him time to ventilate during his office calls. This time does not need to be long nor extensive. Even five minutes of ventilating against neighbors, wife, children, boss or parents can help reduce tension enough and externalize anger sufficiently so that the patient does not need to turn it against his own body.

For the other goal, namely that of helping the patient to gain more affection, the physician can temporarily supply "tender loving care." But in the long run the actual resources in the life of the patient will need to be explored and tapped so that the patient can get insofar as possible, realistic doses of love.

In the case of child patients, the parents must therefore be worked with. They will need to be helped to become more loving. They will need also to learn how to become more acceptant of the child's expressions of anger.

The physician may find, as often happens, that with the ventilation of anger, resources for gaining affection which have not been used heretofore can be used now, since accruing anger ceases to build up barriers so high that affection cannot surmount them even though it is desired as much as it is.

In summary, the skin lesions in infantile eczema, atopic dermatitis and similarly in urticaria represent an unconscious attempt on the part of the patient to resolve an emotional conflict. The conflict lies between his hunger for love, and his anger at not receiving it, with the consequent repression of anger and the turning of it upon himself.

The allergist needs to recognize that the patient's ailment is a continuum of physical and emotional disturbances, linked together by constitutional factors. Insofar as practical, he should make use of his knowledge of the physical aspects of allergy and the emotional aspects within the patient. In some instances his assaying of these various factors will lead him to refer his patients for psychiatric treatment. In other instances he will find that he himself can give them the emotional as well as the physical care they need. In any event, his achievement of desired goals in diagnosis and treatment will be facilitated with another goal realized—namely, with his acquiring some insight into his own emotions. This more than anything else makes clearest his appreciation of the patient from a holistic, psychosomatic point of view.

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Submitted June 23, 1959
Resubmitted September 1, 1959

AN EXPLANATION OF THE LIESEGANG PHENOMENON

Our theory may also throw some light on the formation of immunological precipitate bands in porous media, where it is of great importance to be able to avoid confusion of Liesegang bands with bands due to a multiple immunological system (Wilson and Pringle; Salvinien and Kaminsky; Van Oss, Fontaine, Dhennin, and Fontaine). The mobility of the bands does not necessarily exclude the occurrence of a Liesegang phenomenon, particularly not in the cases where the precipitate is soluble in an excess of one of the reagents, like colloidal and immunological precipitates (Bechhold), and even sometimes precipitates of electrolytes (Pringsheim, and Cetini, and Ricca). The best way to avoid the formation of multiple macroscopical Liesegang bands is to operate with equivalent concentrations of reagents.

Many other phemonena of periodic structure may be explained in a similar way: the very creation of the first structural elements opposes a temporary barrier to the transport of a forming substance. The barrier then loses its function as such for reasons inherent to its growth, thus leaving the way free to the construction of the next structural element. The periodicity is determined by the magnitude of negative feedback arising out of the interaction between the formation and the degeneration of the barrier.—C. J. VAN OSS and P. HIRSCH-AYALON (Van't Hoff Laboratory, University of Utrecht, Utrecht, Netherlands and the Central Institute for Nutrition Research, Utrecht). *Science*, 129:1365 (May 15) 1959.

THE EVALUATION OF SOME OF THE EMOTIONAL FACTORS NOTED IN ECZEMATOUS AND URTICARIAL PATIENTS

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IT IS BECOMING increasingly recognized that emotional factors play a significant role in the etiology of allergic skin disorders. It remains a moot question, however, just what emotions are involved and how they operate to produce the skin pathology.

In the main, two approaches have been used in the investigation of this problem. One group of clinicians, on the basis of statistical data obtained by psychiatric interview, projective tests, and psychotherapeutic trials, have tried to correlate a specific "personality type" with specific dermatoses.[3,10] This, to my mind, has not proved very fruitful. I do not think there is such a thing as an "eczema personality" or an "urticaria personality," nor is it possible to correlate meaningfully any set of overt character traits with any given skin pathology.

The other approach has been to search for a specific constellation of emotional conflicts, such as Franz Alexander has postulated for other psychomatic disorders.[1] How successful has this search been? A survey of the psychoanalytic literature reveals a wide array of psychodynamic conflicts that have a bearing on the skin pathology in patients with psychocutaneous disorders. Flare-ups in the skin symptoms of these patients have been related to an upsurge of sexual desire, which because of guilt cannot be directly discharged. The itching and scratching have been found to have masturbatory significance, while the self-injury represents punishment for the forbidden sexuality.[2] These patients have also been found to be deeply conflicted in the area of aggression and hostility.[4] Any situation which mobilizes anger intensifies their guilt and anxiety and leads to repression of the aggressive impulse. The repressed hostility seeks discharge through the skin. The skin lesion, with its tormenting itching and scratching, lends itself well to the discharge of sado-masochistic urges.[5] It expresses not only aggression turned against the self, but on a deeper psychological level it represents the punishment of and the riddance from a frustrating external love object, ultimately the mother. The skin lends itself readily also for the expression of conflicts around exhibitionism. The exhibitionism, because of its competitive and sexual connotations, is guilt laden. The eruption represents a punishment for the forbidden wish to exhibit and attract, and patients with such skin eruptions suffer from the so-called "leper complex." The eruption

Presented at the Fifteenth Annual Congress of The American College of Allergists, San Francisco, California, on March 20, 1959.

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may also represent weeping into the skin, as is said to be the case in urticaria;[6] while the weeping eruption in eczema may express a plea for mothering and loving care which the patient cannot express verbally and consciously.

Granted the prevalence of these emotional factors in patients with allergic skin manifestations, the question still presents itself: which is the specific emotional constellation which is etiologically significant? Is it the conflict around inhibited sexuality? Is it the repressed hostility? or the conflict over exhibitionism? or the frustrated longing for mothering and dependency? On the basis of the psychoanalytic evidence, I think we must conclude that there is *no* specific set of emotional conflicts which is etiologically specific for the allergic skin disorders. Indeed, we may say without exaggeration that almost any emotional conflict can find expression through the skin, once the skin has become vulnerable to emotional stress.

The problem then becomes: Why do emotional conflicts which are almost universal in their incidence select the skin in these patients for their expression, and how is that brought about? No definitive answers to these fundamental questions are yet available and it will take a great deal of further investigation and experience to arrive at their solution. But a tentative answer to the problem based on psychoanalytic considerations has been advanced.[7] The common factor in all of the emotional conflicts referred to is the production of anxiety. Anxiety in patients with psychosomatic disorders seems to set in motion a regression to infantile modes of handling stimuli, namely along somatic channels. These patients seem to have a weakness in their ego organization, so that they are prone to relinquish the more mature handling of emotional stress by psychological devices and return to the infantile way of dealing with it through autoplastic, somatic reactions.

Since eczema often sets in during the first year of life, the conditioning factors responsible for the vulnerability of these patients to skin reactions must be sought in the mother-child relationship. The mothers of patients with psychosomatic disorders have been found to be overanxious and overprotective, the anxiety concealing an unconscious rejection. The children react to this exaggerated need for control on the part of the mothers with an abnormal clinging and dependency. They never succeed in adequately freeing themselves from this infantile attachment; and whenever in the course of their life any threat arises, whether internal or external, of separation from the mother or a mother-substitute, they react with a somatic illness, through which the dependency is dramatized.

The form which the somatic illness takes depends on a variety of factors. One important determinant of the somatic compliance is to be found in the specific experiences and deprivations to which the child was exposed in the pathogenic mother-child emotional symbiosis, as Melitta Sperling[8] discovered in the simultaneous analyses of twenty mother-child couples.

In this connection, the observations of R. A. Spitz[9] are of considerable interest as indicating a specific determinant for the choice of the skin as the organ for the expression of emotional conflict. He studied the mothers of infants with eczema and found that, because of severe hostility to their children, these mothers were frightened and clumsy when they had to hold their children and did so as little as possible. Consequently these children were deprived of the necessary tactile experiences; their aggressive and libidinal drives, which normally would be discharged in the course of handling by the mother, remained undischarged and sought an outlet in the form of eczematous skin reaction.

If this finding of Spitz's should be confirmed, it would provide an emotional factor which, added to the constitutional and allergic factors, could condition the skin as the site for the future development of a psychocutaneous disorder. Onset and exacerbation of the disease could then be precipitated by a variety of emotional conflicts to which the individual with a predisposition to skin disease is exposed, because these conflicts would link up associatively with frustrations from infancy and childhood. Large amounts of primitive rage could thereby be activated and threaten to overwhelm the ego, which, in order to preserve itself, would be driven into regressive modes of binding anxiety, namely by resomatization through the skin.

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Submitted June 23, 1959
Resubmitted September 25, 1959

MAN

Herbert Ratner, the noted pediatrician of Chicago, has described Nature's high product, Man, as having been turned into a "vitamin eating, anti-acid consuming . . . and surgical-despoiled animal."—*Clin. Phys.*, 1:86 (Fall), 1959.

THE EMOTIONAL FACTORS IN ECZEMA AND URTICARIA

I. Recognition

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THE USE OF immunologic methods in the diagnosis and treatment of chronic urticaria and atopic dermatitis has been generally unsatisfactory. Although patients often present a formidable mass of evidence to substantiate their conviction that foods, fumes, dusts, injected or ingested drugs, contactants and other extrinsic substances are precipitating factors, skin tests or clinical trial with disguised allergens are seldom, if ever, confirmatory. How can conventional allergic methods, so helpful in acute urticaria and contact dermatitis, be so fruitless here?

Chronic urticaria and atopic eczema do not seem to be understandable or explainable as manifestations of the antigen-antibody reaction. Many allergists of long experience are convinced that diagnostic skin testing and dietary manipulation are not helpful in the management of chronic urticaria. Referring to atopic dermatitis, Robert Cooke writes:

> What is needed is more light and a new approach, and my personal opinion is that the work has been hampered by a belief in the diagnostic significance of the immediate wheal-type of skin test, which I have attempted to show and which I believe has no significance in dermatitis.

For several decades now the allergic hypothesis has been tried with little success in these recalcitrant skin disorders.

Some investigators may counter this point of view by reciting case reports of favorable improvement following trial diets, environmental inhalant control, or immunizing injections. Sporadic responses of this type do occur from time to time but are certainly not consistent. Many allergists believe these persistent skin disorders are chronic forms of the acute allergic syndromes, and that a specific extrinsic allergen produces a delayed or cumulative effect. Convincing evidence to support this assumption is, however, lacking. Is the methodology of allergy unsuited to be a measure of these disorders and, if so, what different approach is likely to be more appropriate and more fruitful? My own experience has taught me that psychological methods of diagnosis and treatment afford the physician a rational basis for understanding both chronic urticaria and atopic dermatitis and offers the patient a far greater hope for recovery.

If, then, during the initial history interview and subsequent contacts with these patients, the bias of allergy is laid aside and the patient's thinking, feeling and behavior are evaluated for evidences of emotional stress, the apparently unrelated pieces of the cross-word puzzle fall into

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place. What originally appeared to be an allergic syndrome emerges as a clear-cut picture of psychoneurotic, psychophysiologic or even psychotic disorder. The term pseudoallergy seems appropriate in describing this group of non-seasonal syndromes since most patients seek help from the allergist rather than the psychiatrist.

Characteristically, the patients manifesting pseudo-allergic syndromes have a multiplicity of collateral complaints such as fatigue, nervousness, headaches and bodily disorders of psychophysiologic origin; their personality traits are quite different from the typical allergic patient in that they think and act in an emotional way, making the doctor-patient relationship tenuous and difficult. Initially they resist any inference that the skin disorder is a physical component of a disordered emotional state. They hope the allergist can identify some extrinsic substance to explain their bodily reactions since they are unable or unwilling to accept any personal responsibility for their illness. A few utilize the psychodynamic mechanism of projection to such a degree that they may be classified as paranoid. These problem patients have long been classified among the so-called "intrinsic allergies."

Delusions about the harmful effects of "allergens" are probably as prevalent in the practice of allergy as delusions about poisoned food, noxious odors, electricity, radio and television waves are in hospitalized paranoids. By projecting painful or threatening feelings of fear, anger, or guilt externally, the patient is relieved of responsibility for thoughts and actions which he cannot find acceptable, and anxiety is thereby diminished.

Thus, if the physician's eyes and ears and feelings are attuned to the multiple manifestations of emotional disorder, he will have no difficulty in recognizing that chronic urticaria and atopic dermatitis are bodily manifestations of conflict and stress rather than the result of an obscure allergen difficult to identify. Nor will the physician be fearful of the patient's anger at being told he must assume some measure of responsibility for his illness and for his recovery. Although many patients will reject the opportunity to talk about their intimate personal problems, some will readily accept formal psychotherapy and do surprisingly well. With others the allergist will find he can best serve the patient by assuming the role of the family physician, giving symptomatic relief and emotional support in the hope that with time and repeated life experiences the patient may come to recognize the relationship between his feelings and his symptoms. A few patients will continue to search for the physician who can be manipulated into treating him for something he does not have; that is, for an allergic disorder. When this occurs, physician and patient go hand in hand down a blind alley that can end only in frustration for both, and one more failure is attributed to the allergist and his methods.

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Submitted June 23, 1959

HYDROXYZINE (ATARAX) IN ALLERGIC DISEASES

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THE ETIOLOGY of allergic disorders is complex in nature and influenced by physical and psychic stress. For many years it has been noted that these stress factors may be cyclic in nature, with psychic stress adding to physical discomfort, which in turn adds to psychic stress, and so on. The cycle of allergy is presented succinctly in Figure 1.

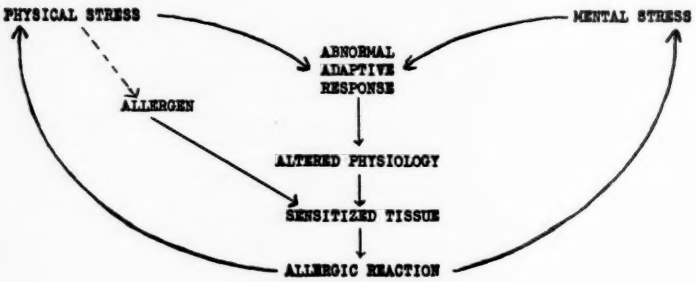

Fig. 1. Cycle of allergy.

Effective control of allergic symptoms is dependent upon the ability of the physician to disrupt the cycle at one or more points. Several methods of control are outlined in Figure 2.

Authors such as Abramson[1] have emphasized the role of emotions in allergic diseases. Accordingly, we theorized that an ataractic agent with antihistaminic properties might effectively control allergic disorders by attacking the allergic cycle at two points: namely, providing release from emotional unrest and counteracting the sensitivity of the tissues involved. To test this theory, we selected hydroxyzine (Atarax)* because of its ataractic and antihistaminic properties and because of its established record of safety during prolonged use.[2,3] It is well known that sedatives and hypnotics, particularly the barbiturates, are effective in controlling the emotional components of allergic disorders and the nervousness encountered as side reactions to commonly used anti-allergic drugs such as epinephrine, ephedrine, and corticoid hormones. These drugs, however

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Presented at the Fourteenth Annual Congress of The American College of Allergists, Atlantic City, New Jersey, April 24, 1958.

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*Supplied by the Medical Department of J. B. Roerig and Company (Div. Chas. Pfizer & Co., Inc.).

have side effects which become more apparent with continued use. With hydroxyzine, we hoped to establish emotional and nervous equanimity, without fear of distressing side effects.

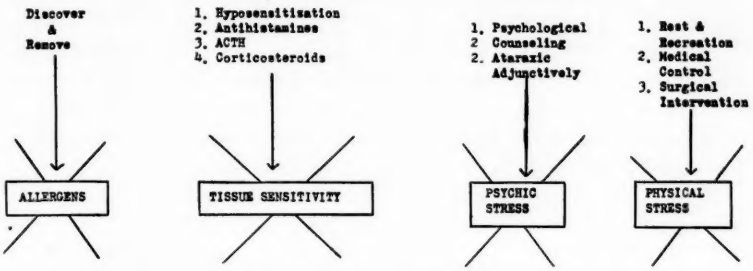

Fig. 2. Allergy control method.

PHARMACOLOGY

The outstanding characteristic of hydroxyzine is the polyvalency of its pharmacodynamic action. Examination of the structural formula (Fig. 3) reveals that it is a hydroxylated etheral derivative of chlorobenzhydryl piperazine. Structurally, it bears a close resemblance to several drugs currently in use as antihistamines; however, alteration of its basic molecular structure has profoundly expanded the applicability of the drug.

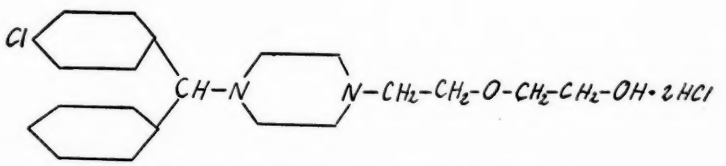

Fig. 3. Hydroxyzine hydrochloride (atarax).

We will cite just a few of its diverse properties: It has antispasmodic properties, blocking the spasmogenic effects of histamine, acetylcholine, serotonin, reserpine, posterior pituitary extract, natural and synthetic oxytocin, highly purified natural pitressin, and barium chloride;[4] it possesses gastric antisecretory effects;[5,6,7] tranquilizes or sedates without producing narcosis;[8] potentiates analgesic agents and central nervous system depressant drugs, and has distinct topical anesthetic properties,[8] antiemetic[8] and anti-vertiginous effects,[9] anti-arrhythmic effects in cardiovascular disease;[10,11] has both primary and secondary muscle relaxing effects;[12,13,14] inhibits the vasopressor effect of epinephrine,[12] and blocks certain behavioral changes induced by mescaline.[15] As an adjunct to anesthesia, it has been used effectively in dentistry,[16] surgery,[17] and obstetrics.[18]

METHOD OF STUDY

Patients for this study were selected from a group who had undergone allergic work-up and who were under standard antiallergic management, including hyposensitization where required. In every case, emotional factors were suspected as keeping the patient out of control or prolonging the condition. We did not attempt initially to control the patient on hydroxyzine alone since we started the study with the precept that hydroxyzine would be only adjunctive therapy to allay the nervous components. In spite of this, three patients recently were completely controlled on this medication alone.

At no time were the patients informed as to the type of medication we had added to their treatment or as to the possible results. Those who required an explanation were told they were getting a new "allergy medicine."

Fifty patients were studied, eighteen men and thirty-two women, ranging in age from two to sixty-eight years, and presenting diagnoses of bronchial asthma, urticaria, atopic dermatitis, migraine, nasal allergy (including perennial allergic rhinitis, hay fever, sinusitis or polyps); also ten reactions to fungus infections, contact dermatitis and allergy involving the urinary bladder. The majority of patients (60 per cent) were under forty years of age. The number of patients and the number of diagnoses were not the same because some patients had more than one allergic condition.

The dosage schedule was kept at 10 to 25 mg. three times a day orally after meals and 25 to 50 mg. at bedtime. The medication was given by injection to initiate therapy in three cases of acute urticaria. The length of therapy varied from two weeks to several months, with four patients remaining on hydroxyzine therapy for over fifteen months. In general, those patients who have been on the drug for longer periods take it only as needed during periods of stress. At no time has there been any need to discontinue therapy because of reactions; the few that complained of drowsiness at the beginning, seemed to tolerate it well as they continued treatment.

RESULTS

Results were evaluated objectively and subjectively, although we had to depend mostly on the reports of the patients. Efficacy was measured in terms of improvement in their sense of well being, decrease in symptoms, decrease in other medications, ability to cope with their daily duties and improved sleeping habits. Table I shows the results.

1. *Bronchial Asthma.*—The results were satisfactory. All patients reported greater calmness and were able to rest and sleep better. None cleared completely, but they needed much less anti-asthmatic medication and led a more normal life.

To illustrate, a thirty-one-year-old man had chronic bronchial asthma and mild emphysema. He was extremely allergic to many inhalants and many foods, as proved by clinical observation and by skin tests. After three weeks of hydroxyzine, the attacks diminished, and he was able to restore to his diet almost every food he had been forced to avoid, though the additions were in small to moderate amounts. His weight and strength increased and his nervousness was quite well controlled.

TABLE I. SUMMARY OF RESULTS WITH HYDROXYZINE

Diagnosis	Number	Controlled	Improved	No Effect
Bronchial asthma	32	0	32	—
Urticaria	6	6	—	—
Atopic dermatitis	10	0	10	—
Migraine	4	4	—	—
Nasal allergy	14	0	Nervousness controlled	14
Contact dermatitis	1	1	—	—
Urogenital allergy	1	1	—	—

2. *Atopic Dermatitis.*—In every case the effect was satisfactory, which is in accordance with the results obtained by other authors.[19] Itching decreased to a minimum and the patients were able to rest well without scratching, with improvement in the appearance of the skin.

A typical example is a fourteen-year-old girl who had had extensive "eczema" since early childhood, during which time she had been seen by many dermatologists. She had been hospitalized many times, had followed strict diets, and had received many forms of local therapy, including x-ray. Skin tests were strongly positive to pollens, molds, house dust, and various epidermals, as well as to yeast, wheat, corn, oats, cocoa, pork and legumes. Her family life was unhappy. The girl appeared ugly and repulsive—her face was raw and swollen and her neck appeared wrinkled and leathery like elephant's skin.

She was started on hyposensitization therapy with elimination of positive foods, a mild ointment and hydroxyzine about September, 1957. The improvement was slow the first month, but her skin started to heal, her morale improved and gradually she became a poised, calm girl. For the past three months, she has been on a full diet and needs no other medication except hydroxyzine at bedtime and occasionally once during the day.

3. *Urticaria and Angioedema.*—The results here were excellent and rather dramatic in all six patients followed—three chronic and three acute. In the acute cases, 25 mg. of hydroxyzine was given by injection then followed with oral therapy. In all cases, there was complete clearance of the skin, very mild symptoms on recurrence, and complete disappearance of itching.

For example, a sixteen-year-old girl had had chronic urticaria for over three years, with acute exacerbations at the time of her menstrual

periods and after ingesting a number of foods. She had been under medical care for a long time and had been kept on strict diets and daily antihistaminic agents. On hydroxyzine therapy, she has been able to follow a general diet and has only an occasional hive at the time of her periods, and during periods of stress. Each spell is completely cleared with hydroxyzine.

TABLE II. SUMMARY OF RESULTS WITH HYDROXYZINE AND PREDNISOLONE

Diagnosis	Number	Controlled	Improved	No Effect
Id. Reactions to fungus infections	3	3	—	—
Severe bronchial asthma	3	3	—	—

4. *Rhinitis.*—Hydroxyzine was not effective in these patients insofar as nasal complaints or changes in the mucosa were concerned. The patients, however, were calmer.

5. *Migraine.*—The results in migraine were satisfactory. By eliminating the anxiety factor, the four patients studied were kept quite free of headaches even though they ingested small to moderate amounts of the foods to which they were sensitive. These results were anticipated and are in accordance with the studies of Unger and Unger[20] on migraine headaches.

HYDROXYZINE-CORTICOSTEROID COMBINATION

In six patients whose conditions also required the use of a steroid, we selected the combination of 10 mg. hydroxyzine with 5 mg. prednisolone (as Ataraxoid*). As shown in Table II, three had severe bronchial asthma and three had generalized ID reactions to fungus infections. We placed the patients on doses equivalent to half the usual recommended steroid dosages. Without exception, the results obtained were excellent in these six patients, and persistently satisfactory even when the doses were decreased to one tablet per day. It would seem, therefore, that the actions of hydroxyzine and prednisolone complemented each other in control of the resistant allergic conditions.

This is well illustrated by the case of a seven-year-old girl who had had a generalized dermatitis since the age of two following a proven and severe fungus infection of the feet. For the ensuing five years, this child had been hospitalized three or four times a year, had seen many doctors, and had received innumerable ointments, injections, antihistaminic agents, and other forms of treatment. On her first visit, the child's skin had an appearance suggestive of a leper. She was placed on the hydroxyzine-prednisolone combination at a dosage of two tablets every eight hours for

*Supplied by Pfizer Laboratories (Div. Chas. Pfizer & Co., Inc.).

one week, then one tablet twice a day for two weeks, then one tablet daily. After twenty-four hours of therapy, the skin was about 50 per cent clear and in three days no evidence of dermatitis could be seen. This child is following a general diet at present and is taking no other medication except one half tablet of the hydroxyzine-corticoid combination daily.

DISCUSSION

We have studied hydroxyzine in allergic diseases since October, 1956. The results have been satisfactory in almost every case where nervousness or anxiety was a factor in initiating, aggravating or prolonging the condition. All cases were proved at the outset to be allergic in nature, and the usual antiallergic management was followed while hydroxyzine was added as adjunctive therapy. Hydroxyzine definitely calmed the patients, caused a decrease of allergic symptoms in most cases, improved the inter-personal relationship of the patients at home, at work or in school, and in most patients permitted a decrease in other medications.

Because of the dramatic results in urticaria, a result which has been independently observed by Feinberg, *et al*[21] in Chicago, Zelcier[22] in Argentina, and Kimmig[23] in Hamburg, we believe the results obtained by the use of hydroxyzine are further demonstration of the polyvalent nature of this ataractic agent. Hydroxyzine combines antihistaminic properties in relieving allergic conditions with muscle-relaxing and tranquilizing effect in allaying the physical and mental stress reactions that accompany these disorders.

We were impressed with the absence of side reactions, except for mild drowsiness in a few patients. There was no evidence of withdrawal symptoms or addiction to the drug. There was, however, return of the original symptoms when hydoxyzine was discontinued.

Since this study was finished, one of us (I.S.) has made hydroxyzine standard therapy in hospitalized allergic patients. Benefits have accrued from better medical management of the patient and less individual attention on the part of the nursing staff.

SUMMARY

Hydroxyzine has been evaluated clinically in several allergic disorders, usually as adjunctive therapy.

1. In all allergic conditions, with the exception of allergic rhinitis, and ID reaction to fungus infection, the drug was effective.
2. In chronic and acute urticaria, hydroxyzine was effective as the sole medicament.
3. Anxiety, nervousness and tension were controlled in almost every instance and even in conditions where the drug was not effective in controlling the primary allergic complaint.
4. We were impressed with the safety and lack of side reactions.
5. The combination of hydroxyzine with prednisolone effectively con-

trolled resistant cases of bronchial asthma and ID reactions to fungus infections.

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THE ALLERGIC INDEX

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NINETY-FIVE per cent of allergic children manifest some evidence of allergy before the age of four years.[1] How many of these early allergic reactions are simply ignored or treated symptomatically as croup or colic or diaper rash is anyone's guess, but it is highly probable, even in this age of enlightened medicine and a knowledgeable public, that many cases of allergy are not diagnosed correctly or treated adequately.

According to the Allergy Foundation of America, there are at present an estimated seventeen million cases of recognized allergy in this country, *most of which began in infancy or early childhood.* It is obvious that the treatment of allergy when it first appears in children carries with it a greater chance of success than does later therapy. Further, in most cases early specific treatment can minimize or obviate the subsequent development of more severe complications and secondary changes.

There can be no question of the gravity of this problem. On the one hand, many general practitioners and pediatricians have come to feel that to the allergist every illness is allergenic, and that each new patient must undergo a thorough program of skin-testing—an attitude which the former physicians rightly refuse to accept. The allergist, on the other hand, is often confronted with the difficulty of first treating his patients after they are far along in the course of their illness, at times so much so that the outcome of his treatment must hang in the balance.

Clein[1] reports that 78 per cent of allergic children show some sign of allergy before the age of four months, while Cohen[2] states that 50 per cent of all children show an allergic reaction before the age of ten years. It is our belief that in the general population the incidence of allergy is probably close to 15 or 20 per cent, and it is this group of 25 to 35 million potential patients that must be diagnosed and treated early enough to achieve the maximum benefits.

In the absence thus far of any feasible method of recognizing all allergic reactions when they first appear, we have formulated a practical set of diagnostic standards—an Allergic Index—to help the examining physician discover the presence or possibility of allergy in infancy or early childhood. Steele[2a] has suggested a "point scoring system" to serve as a guide in *confirming* a suspected case of allergy.

The allergic index represents a weighted mathematical sum of all recog-

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nizable manifestations of the allergic mechanism, calculated in such a manner as to indicate a prognosis of allergy in any individual case. It serves not only to formalize the diagnosis of an allergic tendency, but also—by its very existence—to focus the attention of the physician on the many significant signs of allergy that might otherwise go unnoticed. It will, we hope, help solve many of the problems now complicating the treatment of allergy in children.

TABLE I. ALLERGIC INDEX, TABLE OF SYMPTOM-WEIGHT VALUES

Symptom	*Unit Weight*
Heredity	
Bilateral Inheritance	2
Unilateral Inheritance	1
Bronchial Asthma	5
Colic	1
Chronic Gastroenteritis of Allergic Etiology	1
Infantile Allergic Dermatitis	3
Asthmatic Bronchitis (Bronchitis with Expiratory Wheezing)	
One Attack	1
Two Attacks	2
Three or More Attacks	5
Pollinosis	
One Season	2
Two or More Seasons	3
Recurrent Upper Respiratory Infections	1
If associated with perennial allergic rhinitis or seasonal repetition	2
Perennial Allergic Rhinitis	2
Chronic Allergic Cough (Repeated Tracheobronchitis)	2
Allergic Conjunctivitis	1
Croup, recurrent	1
Bronchiolitis, Two or More Episodes	1
Paroxysmal Sneezing	1
Urticaria	1
Tracheal Clearing, Recurrent	½
Visceral Pain Syndromes, Including Pylorospasm	½
Drug Allergy, Including Henoch's Purpura	½
Migraine	½
Epistaxis, Recurrent	½
Idiopathic Hematuria	½
Canker Sores	½

There are many revealing signs of latent allergy in children. Table I, compiled after an exhaustive review of individual case records and a comprehensive study of the literature, lists them in the order in which they generally present themselves. Each factor has been assigned a numerical weight-value based on its significance in the total allergic picture, its relation to the other symptoms, likelihood of recurrence, familial patterns, et cetera. When the patient's clinical history yields an allergic index, i.e., a numerical total, of five or more units, a diagnosis of clinical allergy must be made and appropriate therapeutic and prophylactic measures instituted.

The role of heredity in the pathogenesis of allergy must be considered first. This factor cannot be overemphasized. The stronger the familial background of allergy, the earlier and more severe will be the allergic

manifestations. Thus, Spain and Cook[3] have reported that 79 per cent of asthmatics with bilateral inheritance and 36 per cent of those with unilateral inheritance develop symptoms during the first decade of life. There is further evidence[4] that the type of allergy present in the parent tends to reappear in the offspring, but this is not always the case. Of course, allergy may also manifest itself in a child without any apparent familial stigma.[5]

The first evidence of allergy in the neonatal period is generally colic or some other type of gastrointestinal disturbance. As has been pointed out by Glaser,[6] the onset of allergy is much more frequent in infants who have colic than in others, even when it could not be proven that the colic was of allergic etiology. Martin[7] also emphasizes the importance of colic in the allergic framework, noting twice as many instances in allergic families as in non-allergic families. When both parents had a history of allergy, the incidence of colic in the offsprings was over 70 per cent.* It should also be noted that infants with a history of colic develop eczema more frequently than other infants.[8]

Colic, although prognostically the most important manifestation of gastrointestinal allergy, may be only one of a number of possible signs of allergy. Considering the nature of the allergic reaction, with edema of mucous membranes and smooth-muscle spasm, it is evident that many other gastrointestinal symptomatologies may be evoked. Glaser has provided an extensive listing of these varied manifestations.[9]

Vague abdominal pain in children may have many causes, ranging from nervous tension to chronic infection. However, when it is associated with repeated symptoms of food intolerance (nausea, diarrhea), excessive mucus secretion, and pertinent family history, it is very probably allergic in etiology.[10] In addition to chronic abdominal pain, the patient may exhibit pylorospasm,[11] and the celiac syndrome.

It has been noted that other allergic manifestations occur in patients with ulcerative colitis to a much higher degree than in the general population.[12] Rothman has described the interrelationships of these factors in his extensive review of gastrointestinal allergy.[13]

Eczema in patients under one year of age or, more specifically, infantile allergic dermatitis, is the next major clinical sign of allergy, and one of the most important manifestations to be considered. A differential diagnosis must be made between allergic dermatitis and a non-allergic disorder such as seborrhea, even though there are many instances of transition from one to the other.[14] From a prognostic point of view, 80 per cent of infants with allergic dermatitis go on to develop other forms of allergy while only 25 per cent of infants with seborrhea show further manifesta-

*Martin reports an incidence of 36 per cent of colic in his practice. This is at variance with the experience of one of the authors (DKA), whose general pediatric practice showed an incidence of 6-7 per cent in a series of 300 consecutive new-borns.

tions.[6] Furthermore, 53 per cent of these infants specifically tend to develop asthma subsequently.[14a]

Other cutaneous manifestations of allergy, while they may be common, do not have the prognostic significance of allergic dermatitis. Contact dermatitis, for example, the most common form of allergic dermatitis in adults, seems to be a manifestation of *superficial* cutaneous allergy. Although it tends to be recurrent and chronic, there is no tendency for it to be complicated by respiratory tract allergy.

Nasal disorders include the next group of allergic syndromes. The chief disorder is often noted in the child who catches "one cold after another" or who "has a cold all the time." It is estimated that approximately one third of allergic children fall into this pattern. Glaser[14] differentiates "perennial allergic rhinitis," in which there is a chronic low-grade mucous membrane irritation, from the recurrent upper-respiratory-infections secondary to allergy. The latter have an episodic pattern, with infection superimposed upon allergy. The characteristic mannerisms of nose-wrinkling and mouth-wrinkling and the so-called "allergic salute" are all attempts to relieve itching and nasal obstructions. Most investigators do not distinguish these two conditions, since in fact they are, pathophysiologically, extensions of the same disorder. However, the recurrent upper-respiratory-infection syndrome is a much more common precursor of bronchial asthma than is perennial recurrent rhinitis. On an overall basis, 42 per cent of these children go on to develop asthma or other major allergy.[14]

In our own experience, perennial allergic rhinitis is a frequent and important disorder. Almost all children who present this syndrome have a strong allergic inheritance and often reveal other evidences of allergy within the first two years of life. Thus we must consider it as another link in the long chain of evidence leading to a definitive diagnosis of allergy.

Although pollen allergy, or pollinosis, is sometimes sought for only in the older child, many investigators have noted its onset in early infancy, particularly in some areas of the country.[15-18] A diagnosis of pollinosis is most often simply based on the periodicity of the symptoms. Frequency of sneezing as a manifestation is emphasized by most authors, but bizarre symptoms such as episodic vulvovaginitis may also arise.

Statistics on the follow-up studies of these patients are impressive. A large number of patients with untreated pollinosis later develop bronchial asthma. Vander Veer,[19] who interested himself principally in the treatment of pollinosis, stated that 30 per cent of untreated hay fever patients develop asthma, while in a practice devoted chiefly to asthmatic children, Peshkin[20] noted that 60 per cent of children with untreated pollinosis subsequently develop asthma. The authors' experience agrees with that of the majority of allergists that adequate treatment of pollinosis provides effective prophylaxis against asthma. If the symptoms increase in severity

from year to year, positive hyposensitization treatment is necessary.

The chronic, persistent, non-productive nocturnal cough which is not accompanied by a nasal or paranasal sinus infection must also be considered a pre-asthmatic symptom.[21,22] Finally, we must take note of a type of pollinosis with symptoms of chest or upper-respiratory-infection developing after the pollen season has ended. The diagnosis of the "masked pollinosis" may be arrived at only after taking a careful and complete history.

It is our experience that many children who are sensitive to one type of pollen antigen readily develop sensitivity to other pollens. This would seem to confirm the belief that once the allergic threshold is lowered, further assaults are more difficult to repel.

The most complex and least clearly delineated of the symptoms of childhood is wheezing. It is unusual to find a clear statement of the differentiation between infection and allergy in this symptom; indeed, there is a large degree of overlap between the two. There are, of course, many causes of wheezing other than allergy. Infection may play an etiologic role. Mechanical factors, such as foreign bodies, organic laryngeal changes, and extrinsic pressure on the tracheo-bronchial tree by tumors of vascular anomalies, must be considered. Further confusion arises from the fact that low-grade fever may accompany uncomplicated bronchial asthma. In almost all cases of asthma there are areas of atelectasis resulting from some obstruction of the bronchi by mucus secretion and spasm. These areas are susceptible to secondary infections, which would account for the fever, leukocytosis, and elevated sedimentation rates commonly seen.

It is a theoretic possibility that repetitive "Asthmatic Bronchitis" either is already or will later become manifest bronchial asthma. It is our belief that it should be treated as bronchial asthma without delay. As regards the allergic index, such other factors as the recurrence of attacks and the presence of other possible signs of allergy must be taken into consideration.

The relationship of hypertrophy and infection of the tonsils and adenoids to allergy in recent years has been clarified. It has been stated that any child who requires the removal of his tonsils or adenoids before the age of three, or in whom a repeat tonsillectomy is necessary, is an allergic child.[23,24] No other stimulus is powerful enough to impose this recurrent and chronic pressure on the lymphoid tissue as chronic allergy. Thus, tonsillectomy because of "recurrent colds" will obviously not lead to relief if the underlying allergy is still present.

There remains a large group of allergic manifestations, some quite common, which play a significant part in the overall evaluation of the patient. These include hives and angioneurotic edema; papular urticaria; drug allergy and idiosyncrasy; Schoenlein-Henoch purpura; and some instances of idiopathic hematuria, migraine, and miscellaneous allergic

reactions of the ear, nose, and throat, including recurrent conjunctivitis and recurrent canker sores. Another significant indication of possible allergic tendency, often overlooked in a general examination, is frequent or recurrent tracheal clearing, or "hawking." Paroxysmal sneezing is usually due to supersensitivity of the nasal mucous membrane and is accepted as a further sign of allergy. Croup, although frequently caused by infection, is twice as common in the allergic individual as in the non-allergic, particularly when food allergy is present.[25]

We must take note here of the strong possibility that many of these symptoms, even though given a relatively low unit value in the allergic index, may of and by themselves indicate a significant and troublesome allergy, requiring *appropriate study and treatment,* if they manifest themselves to a severe degree or if they tend to *recur with frequency.*

In conclusion, we must bear in mind that our most potent weapons in the treatment of allergy are still a thorough history, adequate skin-testing, and specific hyposensitization. Although we should not hesitate to make use of antihistaminics and steroids when they are indicated, let us remember that their indiscriminate use must be considered to be an admission of failure in diagnosis and a clinical mistake that may have serious results.

As to the future, perhaps it lies in the discovery of the role of enzymatic mechanisms, and the use of synthetic substances capable of searching out and destroying allergenic factors, much as penicillinase neutralizes the antigenic effects of penicillin. Or perhaps we shall discover some other means of protection. Only tomorrow can tell.

There has never been any doubt that allergy is a complex problem. It is our earnest hope that our efforts will be of some use in clarifying and placing in their perspective many of the diagnostic and therapeutic factors that have contributed to this complexity.

ACKNOWLEDGMENT

The preparation of this paper has been assisted in part by a grant from The Borden Company, courtesy of Dr. J. F. Muller.

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Submitted June 19, 1959
Resubmitted August 17, 1959

NO ULCEROGENIC EFFECT OF STEROIDS

No positive evidence of any ulcerogenic effect of either adrenocortical steroids or the parathyroid hormone was found in an investigation reported to the annual meeting of the American Gastroenterological Association.

Dr. I. T. Beck of Montreal stated that he and his associates had observed no major changes in uropepsinogen, blood pepsinogen, basal gastric HCl or pepsin in normal human subjects who were treated with 15 mg. prednisone or 75 mg. cortisone for four weeks or 30 mg. prednisolone for one week.

Patients being treated for various diseases with different doses of prednisone for variable periods—one received as much as 1,000 mg. daily—showed secretory values of gastric HCl, pepsin, blood pepsinogen and uropepsinogen no higher than those of normal individuals, Dr. Beck said. Nor were major changes seen in secretory activity of three dogs who received 4 mg./kg. prednisone daily for three weeks.

The investigator concluded that if prednisone does have an ulcerogenic effect, it is not due to increased gastric secretory activity.—*Drug Trade News*, 34:49 (June 15), 1959.

THE IMPORTANCE OF INHALANT MOLD SENSITIVITY IN ATOPIC DERMATITIS

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SUCCESSFUL clinical management of atopic dermatitis implies identification and proper handling of the causative allergens. Food sensitivities are recognized as frequent causes of infantile eczema, but inhalant allergens often assume major importance in the juvenile and adult types of allergic eczema and must be considered in specific therapy. The important role frequently played by atmospheric molds in respiratory allergic diseases has long been known. We wish to present clinical reports which demonstrate the production of atopic dermatitis by inhalant mold sensitivity and the control of these lesions with specific mold therapy.

Hopkins, Kesten and Benham[3] suspected Alternaria as a cause of eczema in one patient in whom it was shown to cause asthma. Kesten[5] found that the persistence of severe eczema occasionally may be associated with respiratory mold sensitivity. Tuft[12] included atmospheric molds among such other inhalant excitants of atopic eczema as pollens and house dust, which he felt are often significant in the childhood and adult age groups. He noted that molds are of greater importance in the Midwestern grain-raising belt of the United States than in regions of lesser mold prevalence. For example, in the Eastern Seaboard area, the incidence of mold sensitivity is about 5 per cent in patients with hay fever or asthma, and, by inference, also in those with atopic dermatitis. Tuft was able to elicit attacks of atopic dermatitis by exposure to a mold and also (as were we) by the injection of its extract, further suggesting a causal relationship.

Jillson and Adami[4] have presented convincing data correlating variations in the concentration of air-borne molds with seasonal patterns of atopic dermatitis. They noted the precipitous drop in outdoor mold counts with complete snow coverage of the ground to explain improvement of dermatological lesions in mold sensitive persons. These authors observed further that seasonal symptomatic variations in atopic eczema in keeping with predictable mold counts strongly suggest sensitization to air-borne fungi. Such associations are of great diagnostic value in the northern part of the United States where meteorological conditions determine definite mold seasons.

Most writers agree that pollens, dust, animal danders and molds must

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This is a collaborative report by members of The Association of Allergists for Mycological Investigations, Incorporated.

Presented at the Fifteenth Annual Congress of The American College of Allergists, San Francisco, California, March 19, 1959.

not be overlooked in the management of atopic dermatitis in patients over the age of two years.[1,2,6,7,14,15] Schiller and Burgin[10] mentioned the possibility that these inhalant allergens might be causes of allergic eczema, but their only specific therapeutic approach was an effort at environmental control with no suggestion of injection treatment. On the other hand Tuft[13] believes that injections of inhalant allergens, including atmospheric mold extracts, are as necessary in the proper management of atopic dermatitis as of bronchial asthma since both conditions are similar in many respects and frequently coexist. In some patients, extremely minute doses of highly diluted mold extracts may be necessary to avoid systemic reactions. These reactions may be delayed for twenty-four to forty-eight hours and if not recognized, may aggravate the dermatological lesions.

Regardless of clinical observations, not all investigators are in agreement concerning the fundamental mechanism in atopic dermatitis. Schiller and Burgin (*op. cit.*), although admitting that inhalant allergens may be etiological factors, felt that proof is lacking of the exact role inhalant substances play in the production of atopic dermatitis. Strauss and Kligman[11] were able to cause exacerbations in existing areas of contact dermatitis by intranasal, subcutaneous and surface applications of specific protein allergens. These authors believed that this was due to fixation of the protein antigens in the sites of inflammation. They contended that, although atopic dermatitis tends to occur in atopic persons, the dermatitis may not be the *result* of atopy. They also concluded that an allergic mechanism may act in a *secondary* manner on any primary dermatitis of unknown origin, and that patients receiving benefit from hyposensitizing injections would be improved not primarily because of such therapy, but possibly by the control of the secondary factor.

Perhaps the most valid explanation of the relationship between atopen and dermatological lesions in reference to the points herein discussed has been offered by Rostenberg.[9] The question of why inhalant molds produce lesions in some individuals cannot, according to Rostenberg, be answered with certainty. In his over-simplified explanation, he suspects an interplay of two factors in all allergic processes: (1) the intrinsic allergenicity of the atopen and (2) the genetic make-up of the patient on whom the atopen is operating. If the allergens, *i.e.*, the atmospheric molds, are of low intrinsic allergenicity, a very special make-up in terms of the patient's genetic composition is required for him to become sensitive to them. Rostenberg rightfully believes that improvement of a dermatitis because of desensitizing injections is *not* evidence that any or all the allergens employed in the injections are responsible for the cutaneous lesions. We support his contention that evidence of this is a flare-up of the dermatitis when the antigen is introduced into a body site other than the involved area.

CASE REPORTS

Case 1.—Mrs. R.W.W., a twenty-seven year old housewife and lifelong resident of the Southwest, had clear skin until the age of four, when she developed mild ante-

cubital and popliteal lesions of atopic eczema. She also had perennial allergic rhinitis. Skin tests done at this time revealed positive reactions for house dust, grass pollens, Alternaria, Hormodendrum, Helminthosporium and Curvularia. Injection therapy was instituted with house dust and grass pollen extracts, and for the molds only Alternaria extract was used because it had produced a somewhat greater reaction than did the other molds. This therapy over a period of ten to twelve years, along with environmental control of house dust and dietary manipulations, gave good relief of the respiratory symptoms, but the dermatitis progressed in severity and distribution of the lesions. There was a noticeable aggravation of the eczematous lesions during the summers, particularly on the occasions when she attended summer camps.

Because of the severity of her dermatitis, this patient was forced to interrupt her freshman year at college. Retesting with molds again revealed reactions to Alternaria, Helminthosporium and Curvularia, and survey data confirmed the significance of the latter two molds in the college town. After the addition of extracts of Helminthosporium and Curvularia to the injections, improvement was immediate and sustained permitting her to return to the same college town without symptoms. Later omission of treatment was associated with a recurrence of dermatitis, but the skin cleared again following resumption of regular injections.

The successful therapeutic result in this patient emphasizes our contention[8] that significant genus specificity may exist within such closely related genera as those of the family *Dematiaceae,* and when this occurs, species of one genus, such as the genus Alternaria, may not be sufficiently cross-reactive with species of the other genera to constitute an adequate "key" or "family" allergen. The reactions to Helminthosporium and Curvularia had been observed twelve years earlier, but their appearance with the more reliable acetone precipitated ("type 33") extracts used in the retesting suggested their importance for the first time.

Case 2.—Mrs. R.R., a twenty-eight year old housewife and resident of the Midwest most of her life, had suffered from adult type atopic dermatitis for twenty-two years; she also had bronchial asthma. In childhood, the dermatitis and asthma had been perennial, although not constant, but for several years both complaints were limited to the period corresponding to the Midwestern mold season from April or May until late November. Spontaneous improvement of all symptoms had occurred during a residence of eighteen months in Connecticut. This patient suspected aggravation of both the dermatitis and respiratory distress upon exposure to dusty or moldy environments, but previous injections of house dust extract had failed to produce improvement.

Skin tests revealed markedly positive reactions to Helminthosporium, house dust, and wheat. Treatment included instructions for the environmental control of house dust, elimination of wheat from the diet, and hyposensitizing injections of house dust and Helminthosporium extracts administered perennially. Aggravation of the dermatitis with characteristic lesions has occurred within twenty-four to thirty-six hours after the administration of Helminthosporium extract in dosage exceeding her tolerance. Except for these aggravations, she has remained well as long as injections are continued.

Of interest is the observation that this patient, although still clinically sensitive to Helminthosporium, now fails to show skin test evidence of such sensitivity. The wheat sensitivity proved to be of significance only in the respiratory discomfort.

Case 3.—J.R., a twenty-six year old Midwestern farmer, suffered from atopic dermatitis in early childhood. No causes were discovered for these earlier attacks which eventually cleared spontaneously over a period of several years. In January, 1957, he experienced a return of the eruption with progression to generalized involvement

characteristic of the adult type of atopic dermatitis. He also had had perennial allergic rhinitis for the preceding four or five years with questionable aggravation in the spring and fall.

Studies revealed scratch test reactions for house dust and several molds of the dematiaceous group, including Alternaria, Hormodendrum, Helminthosporium, Curvularia and Stemphylium. Treatment consisting of environmental house dust control and injections of a mixture of the reacting molds was instituted in December, 1957, with progressive clearing of the dermatitis by March, 1958. The respiratory complaints were unaffected by injections of the mold mixture, but they have since responded to the addition of house dust extract to the treatment injections.

This patient has reported exacerbations of his dermatitis after working with grain at harvest time, or in preparing animal feed mixtures. He also experienced an acute flaring of his skin lesions with an overdose of mold extract, but with a slower increase in dosage he has ultimately been able to tolerate greater amounts without symptoms of local or generalized reaction. His skin was clear when he was last seen in October, 1958.

Case 4.—Mrs. A.A., a thirty year old Midwestern housewife was first seen in early 1958. Since early childhood she had suffered from perennial bronchial asthma and atopic dermatitis, neither of which had responded to previous therapeutic efforts. There was an increase in severity of the asthmatic symptoms during heavy concentrations of atmospheric molds, but no aggravation of the dermatitis. Skin tests were positive for house dust, *Rhizopus nigricans,* Helminthosporium, Hormodendrum, and *Nigrospora sphaerica.*

With injections of extracts of house dust and of the reacting molds, this patient has experienced progressive clinical relief.

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Submitted April 2, 1959

Resubmitted October 12, 1959

ASTHMA CAUSED BY IPECACUANHA

Historical Document

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To the Editor of the *Boston Medical and Surgical Journal.*

SIR,—In the last No. of the *Western Journal of Medicine and Surgery,* I notice a communication by Dr. Robertson, of Nashville, entitled "Singular Effects of Ipecacuanha," illustrated by the writer's own case. Having been myself a sufferer from these "singular effects," I take the liberty to send you the results of my experience and observation on the subject, that in the mouth of two or three witnesses the matter may be established, and with a hope that it may aid in preventing my medical brethren from suffering or inflicting on others a similar misfortune. I have delayed the publication for years, for no other reason, that I am aware, than that no man willingly calls up or dwells upon painful scenes.

New York, Oct., 1843. Yours, &c., URIAH TURNER, M.D.

I inherited from my mother's family, with a slender constitution, a strongly-marked nervous temperament; and with advancing years, dyspepsia, with its long train of attendants, developed itself, but without any disorder of the respiratory organs until my 25th year.

Late in the autumn of 1822, while attending medical lectures, I was seized, after a night of exposure, with a pretty severe pneumonia, which confined me about two weeks. Under the care of the venerable Professor Nathan Smith, I was treated principally with antimonials, bleeding being deemed unnecessary; and after my recovery, which was rapid, my health continued as formerly, until the spring following, when I commenced the practice of medicine in Litchfield Co., Conn. During the spring and summer I had repeated and severe attacks of spasmodic asthma; arising, as I then supposed, from the exposure incident to my employment, acting on my lungs, rendered susceptible by the previous pneumonic attack. The paroxysms usually came on suddenly, preceded by tickling in the nostrils, and sneezing, and continued from three days to three weeks, during which I was unable to remain in a recumbent position. During a paroxysm, the dyspeptic symptoms were usually mitigated considerably.

In the autumn following, more than six months from the first attack, I was led for the first time, by mere accident, to attribute these asthmatic paroxysms to the irritating properties of ipecac, when inhaled, having never read or heard of anything to guide my investigations. I was in the habit of using ipecacuanha freely in my practice, both alone and in combination, which, like most country practitioners, I carried with me and dealt out at the bedside. Having occasion, during a violent storm, to visit a patient who could not afford the light of a candle, I was obliged to make use of the floor for a table, and the "fire fair blazing" for a

Reprinted from *The Boston Medical and Surgical Journal,* Vol. XXIX, No. 12, Wednesday, October 25, 1843.

lamp, and in the course of this awkward operation, a large paper of ipecac. was broken open, and scattered freely through the room. After the usual preliminaries of sneezing, etc., I found myself laboring under an unusually severe paroxysm of asthma, which, as formerly, I attributed to the inclemency of the weather; but while pursuing my lonely way homeward, amid the pelting of the storm, leaning forward in the carriage in order to breathe, and obliged to trust my horse to his own discretion, I became suddenly sensible of smelling and tasting ipecac., with a slight degree of nausea, and before I reached my residence, the truth flashed across my mind that all my sufferings might have been caused by this drug. My attention once properly directed, I soon established the fact beyond all doubt by actual and painful experiment. Yet so new and singular was the fact, that it was a long period before I could convince myself that even a single grain floating in the atmosphere of an ordinary room, was capable of inducing a violent paroxysm of asthma, continuing weeks, preventing a recumbent position, reducing the strength as rapidly as an ordinary fever, and only terminating by cough and expectoration. Ipecacuanha being so constantly required in practice, I attempted every means to handle it with safety—using extreme care, covering my mouth, etc.; but with all these precautions, accident or haste rendered them not unfrequently unavailing. A bit of paper in which a Dover's powder had been wrapped, stepping into a physician's office, or even coming in contact with his clothing, might and often did cause a paroxysm sufficient to arrest me in the midst of my business, and to render my services at all times precarious; although for years I kept the article in a separate closet, and in no case presumed to handle it myself.

Such are some of the effects of inhaling the powder of ipecacuanha—one of our mildest and most useful remedies—effects essentially different from that of any other article with which I have ever come in contact. The fumes of burning sulphur often produce a sudden dyspnoea, but it continues only for a few minutes, and in severity bears no comparison to that resulting from epecac.

But like Dr. R., I, too, have suffered the horrors of taking an ipecac. emetic—the recollection of which, at a distance of almost twenty years, thrills through my nerves like some hideous and long-remembered dream. These effects, however, differed in some essential particulars from those described by Dr. R., as will be seen in the sequel.

Early in the spring of 1825, I took half a drachm of powdered ipecac root, in tepid water, taking the precaution to have it weighed and mixed in a part of the house remote from my own room, not dreaming that any other form than dry powder would affect my breathing. Sad mistake! showing conclusively that the peculiar deleterious effect of this drug depends on an idiosyncrasy, and is in no way related to that usually produced on asthmatics by dust, feathers, etc. To proceed. In about

the usual time for an emetic to operate, there seemed to be a simultaneous effort to breathe, cough and vomit, while neither of these functions was performed in any degree of perfection—producing a state of suffering totally indescribable by words. The peculiar *burning* sensation mentioned by Dr. R. is not so distinctly recollected, but the whole muscles of the chest and abdomen seemed in a state of violent irregular spasm—every effort to vomit being interrupted by an attempt to cough; and notwithstanding a cold March wind was blowing, it became necessary to open the windows and support me in an erect position for nearly an hour, to prevent immediate suffocation—an event momentarily expected by myself and friends. At the end of about an hour, without any previous mitigation of symptoms, I was almost instantaneously and completely relieved, and at my own request was laid upon the bed. My breathing was free and natural, attended, however, with extreme weakness; at the same time a burning heat was diffused over the whole surface of the body, which, on examination, was found to proceed from a kind of erysipelatous eruption covering every portion, similar to what is seen after exposing the naked skin to a burning sun. The patches were circular, and varied from the size of a sixpence to that of the palm of the hand—considerably elevated, with thick rounded edges, and of a fiery color. Yet so much greater had been the previous suffering, that the burning did not prevent me from soon falling into a profound sleep, which lasted until morning; and, what is remarkable, there was no return of the asthmatic symptoms; whereas, in every other instance where they were brought on by ipecac, they have continued several days at the least—thus rendering it almost certain that suffocation was prevented by one of those numerous resources which Nature, or, to speak as a Christian philosopher, Nature's God, has always at hand when the puny art of man has failed.

In several subsequent years I experienced numerous attacks without always being able to trace them to any specific cause. On two occasions I took a single laxative pill, without being aware that each of them contained about a grain of ipecac.; yet in both instances, after an interval of eight or ten hours, a severe paroxysm of asthma followed their exhibition, and continued several days. In both cases the pill was taken on going to bed, rendering it impossible to attribute the result to any other cause.

With respect to remedies, a large dose of morphine or chloric ether taken at the commencement of a paroxysm, appeared to mitigate the symptoms. Smoking tobacco freely had a similar effect, while smoking the stramonium root seemed rather injurious. Lobelia, in form of tincture, produced an irritation somewhat like ipecac.

I suffered two attacks from exposure to ipecac., of such unusual violence as to deserve notice. Instead of the ordinary wheezing, the muscles of respiration seemed tetanically convulsed, producing a condition not unlike what is denominated "holding the breath," with sighs or catches at

intervals barely sufficient to keep the wheels of life from ceasing altogether. In the first instance relief was obtained by swallowing two drachms of *eth. sulph.*, leaving instead a singular but pleasing mental excitement. In the other, where the interrupted breathing had continued fearfully long, and where swallowing was impossible, inhaling the fumes of burning paper previously saturated with *nitras potass.* alleviated the symptoms almost instantaneously.*

Such are the brief outlines of my own case, which I have reason to believe will be new to a majority of the profession; but my attention having been much directed to the subject, it may be proper to state that four other cases of a similar character have come to my knowledge, rendering it probable that strict observation will discover many others, who may have suffered without knowing the cause. With two of the persons alluded to, wives of physicians, I am intimately acquainted, and am informed by them, that so far as they believe, they have never suffered asthma from any other cause than ipecacuanha, either inhaled or taken as an emetic—the latter producing most violent effects on the respiratory organs. The subjects of the two other cases were physicians, from whose medical friends I received the account.

From a long and careful consideration of all the circumstances above detailed, I have derived the following conclusions:

1. That in my own case the susceptibility to the irritating qualities of ipecacuanha was entirely created by the pneumonic attack—an opinion which derives strength from the fact that while a student I was in the daily habit of handling it freely.

2. That no asthmatic symptoms would have followed the pneumonia, had I not been exposed to this powerful agent. But that,

3. The habit once established, and the lungs having taken on the asthmatic action, the ordinary exciting causes of the disease, cold, watchfulness, etc., had the power of prolonging, and ultimately of inducing it.

4. That all asthmatics are liable to suffer from coming in contact with, or in any way using, ipecac. Hence physicians cannot be too cautious how they prescribe it for patients having the least tendency to asthma, as distressing and even fatal effects may follow its administration.

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*This remedy was communicated to me by the late venerable President Harris, of Columbia College, who informed me that through a long life he had been unable to sleep without filling his room with this vapor; and there are many asthmatics to whom I have recommended it, who derive great benefit from smoking or burning it in their sleeping apartments.

Progress in Allergy

THE DOUBLE-BLIND METHOD OF DRUG EVALUATION

A Critical Review

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IN MESOPOTAMIA, "the cradle of civilization," 4,000 years ago, drugs, together with physiotherapy, prayer, animal sacrifices, and exorcism, were employed in the treatment of disease. As the concept of the causes of disease progressed from demonology through the wrath of a righteous god as punishment for sin, then metaphysical medicine, and finally to that of universality of natural law, the type of therapy changed to fit etiologic theories, but always included drugs.[1] Through the centuries, drug indications were based on mysticism, superstition, coincidence, casual inadvertencies, fortuitous or supposedly fortuitous accidents, religious tenets, and the unquestioning acceptance of authoritarian dogmas. With the appearance of more modern attitudes in medicine at the end of the last century, and with the development of pharmacology as a scientific discipline, it became possible to question drug action and effects.

Unfortunately, unthinking acceptance of supposedly incontestable doctrines persists in this modern era. Text after text, article after article repeats and re-affirms outmoded therapies, based on drugs which have never been adequately evaluated. Some drugs have a "reputation," often undeservedly. Fortunately, it appears that unquestioning concurrence in and perfunctory reiteration of past judgments on the therapeutic actions of drugs are on the wane.

The purpose of this paper is to review critically one of the methods of evaluating drugs. Drugs to be accepted by the profession should possess real therapeutic efficacy, represent an improvement over existing preparations, and offer benefits outweighing the potential risk of their administration.

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THE SCOPE OF THE PROBLEM

Recent years have seen the development of rapidly increasing numbers of drugs of increasing potency, growing specificity, and heightened effectiveness, encompassing a multitude of physiologic and pharmalogic actions. Synthetic methods of drug preparation, pharmacodynamic predictions of drug effects on the basis of their molecular formulae, exploitation of whole series of related compounds, and modifications of molecular structure to achieve wanted ends characterize recent pharmaceutic effort and add to the difficulties of using drugs in practice. The daily mail, advertisements in medical journals, and books and periodicals having as their sole function the listing of claims made for "new" drugs amply attest to this situation. Alleged excesses and abuses in the promotion of these new medicaments are the subject of a recent series of four articles in a lay magazine,[2] in which the author, a science editor, is so aroused as to suggest that drug advertising be scrutinized by Congress and that perhaps remedial legislation might well follow. A prominent medical journal has also recently taken up the cudgels regarding drug advertising in a more restrained and constructive manner.[3,4]

The potent new drugs possess increased potential for harm, by allergic, endocrine, or toxic mechanisms, by disturbing homeostasis, or by manifesting objectionable pharmacologic effects in addition to their laudable ones. As extensive study is required to delineate the relative frequency and severity of these actions—the "side effects"—as is needed to define the clinical effectiveness of the compound. The value of a drug in practice is determined by subtracting the chance of these unwanted consequences from the potential good to be accomplished, with due consideration of the nature and clinical course of the disease being treated.

In view of the difficulties of making such calculations, and in view of the multiplicity of medicinal agents and therapeutic approaches now available, is it any wonder that several physicians contemplating a single patient will often disagree about his treatment? A chronic asthmatic may be a candidate for adrenocortical steroids, antibiotics, tranquilizers, aerosolized bronchodilators or wetting agents by intermittent positive pressure breathing techniques, in addition to all the older and well-established therapy. In the end, each physician makes up his mind on the basis of his own necessarily limited experience, his acquaintance with the scientific literature, and quite probably a host of prejudices, presumptions and misconceptions. A firm, objective, reliable evaluation of each drug and a clear delineation of its indications and limitations is needed. Hodgkins[5] states that the clinical trial resolves itself into three factors: careful planning, conscientious performance and honest and courageous interpretation of the results.

What of the medical literature? How many laudatory articles have acclaimed new drugs with great enthusiasm only to have them fall by the wayside, usually because of lack of effectiveness? More critical and

more objective evaluation of drugs is needed before they are advertised and made available to the profession.

Even the most painstaking animal studies leave much to be learned about the value and potential dangers of a drug in the treatment of human beings. The animal findings merely suggest the areas in which a drug may prove useful. Species differences exist and, in addition, most of the pharmacologic data are gathered on normal animals whereas the physician administers the drug to a sick human being. The ultimate test is the test in the patient. Detection of side-effects, mild, serious or fatal, usually requires evaluation in the human subject. Some side-effects do not appear in the experimental animal and others, being subjective, such as nausea, anorexia, impairment of reasoning, memory and vigilance, cannot be reported except by human beings.

Recognition of these problems is noted in the attempts of pharmaceutical manufacturers to submit new products to more or less adequate clinical trials, and in official actions of the Council on Pharmacy and Chemistry of the American Medical Association,[6] the British Pharmacological Society,[7] and the Royal Society of Medicine.[8] In fact, the Council on Drugs has as its purpose "to provide physicians with authoritative statements on new drugs as soon as possible after they are placed on the market, obviating the necessity of the physician's relying solely on the manufacturer's advertising material for concise information about the product."[9]

However, one of the reviewers was recently impressed with the contrast between the excellent animal studies and the completely inadequate clinical trials in a report on a new drug forwarded to him for evaluation by the Council on Drugs of the American Medical Association. This material, submitted to the Food and Drug Administration in a request for release of the drug, encompassed only simple, uncontrolled clinical usage in a wide variety of conditions. One of the investigators, an outstanding research man with a world-wide reputation, stated in his covering letter: "I really feel quite uncertain about such evaluations. I suppose this material is as good as any other. I hope you can make something out of this rather mushy data." If by "any other" the investigator means any other method of clinical drug evaluation, we heartily disagree. If he means any of the other clinical reports submitted in the booklet, we, as practicing physicians interested in good medication for our patients, shamefacedly agree with him.

CLINICAL EVALUATION OF DRUGS

The mere fact that a patient's disease is controlled or alleviated, or that his symptoms abate while he is taking a drug is no indication that the drug is responsible. We physicians fail to remember that *post hoc; ergo propter hoc* is a demonstration of a fallacy, not a truth. Haggard[10] credits the philosopher Kant with originating this phrase, and considers it "the root of quackery and mistakes" and "the greatest source of human error."

Many illnesses, many symptoms of illness, and many acute episodes occurring in the course of chronic disease are self-limited. In addition, far reaching and important psychic influences attend examination by a physician and his writing a prescription. Patients often say, "I feel better just seeing my doctor." Someone is taking an interest in him and in his medical problem, and an attempt is being made to help him. Many patients have a mystical, almost a magical faith in a drug therapy. For these reasons, symptomatic benefit may ensue whether or not the drug is an effective pharmacologic agent. We agree with Kligman[11] when he says, "Patient satisfaction is not a reliable measure of efficacy. Inert materials give good clinical results in a high proportion." We shall not pursue the psychodynamics of this phenomenon, the position of the physician as a "father image" and the psychic components of all disease. But these factors play a significant part in drug therapy. In drug evaluation, they must be compensated for if a true picture is to be obtained.

The pragmatic physician may ask, "What's the difference whether the drug is really effective or not, so long as my patient improves?" In the individual patient under treatment it makes little or no difference, but the evaluation of a new drug must be viewed differently. The investigator must attempt to eliminate all extraneous elements so that his evaluation will have universal applicability—the drug acts not because of unrelated and irrelevant circumstances, but because of its pharmacologic effects on the human organism. Simple clinical impression, Beecher[12] says, is "hardly a dependable source of information . . . [and] safeguards are essential when matters of judgment enter into decision."

Many a new drug is introduced by articles in the medical literature hailing it as a great advance, only to be found of little or no value within a short time. Modell[13] points out that drug manufacturers never publish obituaries on dead drugs, for they continue profitable since the words printed years ago continue to sell them even after they have been found to be without value. Advertisements often refer to old and disproved studies. The original favorable opinions were gained in noncritical studies based on "clinical impression." The investigators were misled by their own enthusiasm for the product, or by a natural bias to favor a new product in which they were interested, or by either deliberate or unconscious transfer to the trial subjects of their own attitudes, or, perhaps, by the inclination of patients to provide their physicians with the answers which they think are wanted. Two excellent examples of a physician's attitudes influencing the apparent action of drugs, as demonstrated in controlled studies, have been contributed by Kast and Loesch[14] and Shapiro et al.[15]

The term bias, in the statistical sense, does not imply deliberate or malicious action. It is rather the inclusion of any uncontrolled or unrecognized factor or factors which, by acting in a given direction, may

affect the results of the investigation.[16] (In addition, in the more commonly accepted sense, it may mean conscious or unconscious prejudices or feelings regarding the anticipated results, and these may so sway the investigator as to gravely distort the reported findings.) Simple examples of statistical bias, often exercising a definite influence on the data, are the sex- and age-distribution of the case material, seasonal determinants, self-selection by volunteers, and the like. It appears in more subtle form in the registration of subjects for reasons of easy accessibility or convenience, or in unrecognized socio-economic influences on the outcome of the study. Examples are given by Hill[17] and in other statistical texts. Bias may also result from absence of or inadequate controls. It is, in one sense, the opposite of randomness, a concept requiring that the experimental sample reflect the characteristics of and be representative of the population (in statistical terms, "the universe") to which it belongs. This aim is accomplished by randomization, which in the true probabilistic sense is not haphazard. It may be defined as a systematic process of selection, giving to each member of a population an equal chance of being chosen. "Moreover, an element of randomness in the allocation of subjects to treatments is strictly a prerequisite for the use of standard methods of statistical analysis, and any neglect of this will necessitate special explanations even if it does not invalidate the experiment" (Finney[18]). Bias is a form of selection, and a selected sample is not representative, whether the bias is due to deliberate choice or to unconscious selection of the members incorporated in the sample.[17] "The human mind, unaided or unguided, has a tendency away from real randomness."[19] Sources of bias may be avoided, distributed, measured or interpreted. No uncontrolled study and few clinical ones have taken any of these factors into consideration.

Modell[13] points out that whenever medication is given a patient (in fact, when almost anything is done), controls are used in some frame of reference. The physician compares the degree of improvement of his current patient with that of previous patients under different treatment just as the housewife compares the flavor of tonight's meat dish with that of last week which was seasoned differently and as the driver compares his time to town on the new expressway against his time using the old streets. There is no such thing as an uncontrolled experiment. The essential requisite is that the controls be well thought out, valid, and suitable, thereby leading to reliable conclusions.

It is in an effort to provide for this type of control and, to some extent, to measure the scope of the non-essential influences that the double-blind method of drug evaluation has arisen. The methodology was first clearly described by Denton and Beecher[20] and by Keats, Beecher and Mosteller.[21]

THE DOUBLE-BLIND METHOD: TECHNIQUE AND APPLICATION

In the double-blind method, neither the patient nor the investigator is aware of which preparation is the active drug (the unknown) and which is the placebo (inert preparation). Both participants in the experiment are "blind"— hence the designation, "double-blind"— in contrast to the situation in which the subject is not informed although the investigator knows —the "single-blind" method.

To maintain the uninformed status of both participants, the two preparations are identical in appearance and taste,* and are labeled with a non-informative coded designation. (With certain forms of treatment such as surgery, general anesthesia, and psychotherapy, such expedients are not possible. But this rarely applies to drug trials.) The two preparations are administered in sequence to each trial subject so that each patient acts as his own control during a control period of the same length as the trial period. This obviates the problem of obtaining a separate matched control group with all the difficulties involved in age and sex distribution, severity and phase of the disease, and the like. The order of administration of the active drug and the supposedly inert placebo (the pharmacologic effects of which will be considered below) is randomized to eliminate any reciprocal effects produced by the order of their administration, changes with time, et cetera. The duration of each period of observation depends on the anticipated speed of action of the medication.

All pertinent data are recorded at intervals determined by a number of factors during the periods of observation. Only after all the data have been collated may the "key" revealing the identity of the active drug and the placebo be made available to the investigator. The data should, in almost all instances, be subjected to statistical evaluation.

Various modifications of technique have been employed. Multiple coding, in which each preparation is labeled with any one of several uninformative designations, has been used to prevent the investigator from inferring early in the course of the experiment which preparation is which. Color-coded tablets were employed by Schiller et al[22-24] who found that no bias of importance was introduced by this and that the administration was simplified. In numerous recent studies one or more drugs of known activity and therapeutic efficacy have been incorporated for comparison with the new preparation and with the placebo. Another useful variation involves the use of each medication at more than one dosage level. Multiple placebos, involving two or more control periods for each subject, have been employed in some experiments, but this prolongs and complicates the study and is not often necessary. In the evaluation of medications for topical application to the skin, simultaneous administration of the two

*Difficulties are occasionally encountered in disguising the placebo for certain liquid preparations, and patients holding tablets in their mouths have been known to detect differences in taste.

preparations is made to two different symmetrical skin sites (the paired comparison method[25]).

Beecher[26] has summarized the procedures essential to the proper appraisal of drugs designed to modify subjective effects and symptoms as follows: (1) a group of co-operative individuals who report on the response under study, (2) arbitrary but clear criteria of effectiveness of a given drug, (3) the "double unknowns" technique, (4) the use of placebos also as "double unknowns," (5) the use of a standard or reference for comparison, (6) randomization of order, (7) correlated data, and (8) mathematical validation of differences.

As noted above, a placebo is used in the control period. According to Gaddum,[27] the word placebo has been in use since 1811, although the concept certainly was employed by physicians prior to that time. Gaddum prefers to call the inert preparation dummy tablets, while others refer to them as blanks. The administration by the physician of pharmacologically inactive substances is not without clinical effect. Numerous articles by Beecher and his colleagues in the past decade have explored this subject intensively. One of these[12] may be quoted at some length:

"It is evident that placebos have a high degree of therapeutic effectiveness in treating subjective responses, decided improvement, interpreted under the unknowns technique as a real therapeutic effect, being produced in 35.2 $\pm$ 2.2% of cases. This is shown in over 1,000 patients in 15 studies covering a wide variety of areas: wound pain, the pain of angina pectoris, headache, nausea, phenomena related to cough and to drug induced mood changes, anxiety and tension, and finally the common cold, a wide spread of human ailments where subjective factors enter. The relative constancy of the placebo effect over a fairly wide assortment of subjective responses suggest that a fundamental mechanism in common is operating. . . . The evidence is that placebos are most effective when the stress is greatest. . . .

"Placebos have not only remarkable therapeutic power but also toxic effects. These are both subjective and objective. The reaction (psychological) component of suffering has power to produce gross physical change. It is plain not only that therapeutic power of a drug under study must in most cases be hedged about by controls . . . but also that studies of side-effects must be subjected to the same controls." Impressive examples of the potency of placebos have been described by Wolff et al,[28] Wolf,[29] and Traut and Passarelli.[30] Wolf[29] showed that placebos can not only modify the action of effective drugs in either direction, but that alone they may produce pharmacologic effects with measurable changes at times more potent than those due to the active agents. Even so persistent a condition as chronic rheumatoid arthritis may be influenced in a significant proportion of cases by placebos.[30]

The extent to which an inert placebo (lactose) can give rise to side effects and even "toxic" reactions has been interestingly documented by

Wolf and Pinsky.[31] From ten to twenty per cent of the patients were worse on taking either the active material (mephenesin) or the placebo, mostly from minor or equivocal complaints such as lightheadedness, drowsiness or anorexia. Three of the thirty-one patients had "major reactions," including sudden overwhelming weakness, palpitation and nausea in one instance, a typical dermatitis medicamentosa in another, and epigastric pain followed by watery diarrhea, urticaria and angioneurotic edema of the lips in the third. Although "conditioning" by prior administration of the active preparation may influence the occurrence of some side-effects from the placebo, this phenomenon does not account for all such instances. These observations indicate the necessity for randomization of the order of administration of the trial compounds.

It then becomes clear why placebo controls are necessary in evaluating both the efficacy of a new drug and its incidence of side-effects. If the influence of the placebo-reactors (those individuals who obtain relief or manifest side-effects from an inert substance) on the data obtained in a clinical trial is not taken into consideration, grave errors may be made in the evaluation of the new preparation. The placebo control period assesses the influence of the doctor-patient relationship, the effects of "taking medicine," the psychologic effect of being "cared for" and other intangibles which affect therapeutic results. By comparing the efficacy of the active drug with such a "base-line" or, alternatively, by removing the placebo reactors from the data, a truer estimation of the effects of the unknown drug is reached.

Certain drug trials obviously do not require double-blind technique. Where a medication is dramatically effective, reversing the signs of morbidity in a high percentage of subjects or, in some diseases, reducing mortality to an impressive degree, one would not need controls. However, a misconception exists that when the effect may be measured objectively or quantitatively, the double blind technique is unnecessary. This is erroneous. Hypertension, measured by the sphygmomanometer in numbers, is influenced by many factors,[32,33] both physical and psychologic. The same holds true for obesity, measured by numbers on a scale. The ability to conceive is known to be influenced by many factors, so that despite the fact that pregnancy is an objective (and obvious) condition, study of the effect of contraceptives[33a] and of treatment for sterility should also be controlled. Thus, any manifestation which may be affected by a variety of factors requires the controls of the double-blind method, irrespective of the manner of evaluation, subjective or objective, qualitative or quantitative. Moreover, the quantitative measurement itself may be altered in accordance with the investigator's bias. Modell[13] states, "Even a laboratory man reading a colorimeter may be influenced by what he expects to find."

To prevent bias in selection of patients, based possibly on favoritism, and for other reasons, the double-blind method was considered necessary

in the field trials of gamma globulin for poliomyelitis prophylaxis, in the first large-scale trial of the Salk poliomyelitis vaccine, and more recently in the study[34] of orally administered live attenuated poliovirus vaccine.

Beecher[35] has listed nine classes of drugs with which controlled evaluation studies are important: sedatives, hypnotics, analgesics, ego-depressants, anesthetics, antimetics, antitussives, antipruritics, and euphoretics or tranquilizers. We feel that there are many others, including those exhibiting effects which allow the use of objective and quantitative yardsticks. As early as 1948, the British Medical Research Council felt it desirable to subject an investigation of streptomycin in the treatment of pulmonary tuberculosis to at least a single-blind study.[36]

The broad scope of applicability of the double-blind method can be indicated by citing some of the recent publications employing this method. They include appraisals of the effects of anorexigenic agents[37-39] and liothyronine[40] for weight reduction; amphetamine sulfate[41,42] on athletic performance; hypotensive agents[32,33,43,44] for essential hypertension; antitussives[45-47] for cough, with the response objectively recorded by an impartial but "blind" observer; narcotics, pentobarbital and amphetamine[48] on mood changes objectively determined by psychologic interviews and Rorschach tests; topical steroid preparations[49-53] in inflammatory dermatoses; triacetin[54] for superficial dermatomycoses; morphine by injection for postoperative pain;[55] buffered aspirin for rheumatoid arthritis;[56] salicylamide and aspirin as analgesic and antirheumatic agents;[57] codeine and propoxyphene hydrochloride for chronic pain;[58] buffered and nonbuffered acetylsalicylic acid for various painful conditions,[59] musculoskeletal pain,[60] and both;[61] analgesics;[62-64] morphine for postoperative wound pain and experimentally induced pain;[65] bronchodilators for asthma and other obstructive pulmonary diseases, with or without emphysema;[22,23,66] antihistaminic drugs for colds and sulfonamides for sore throat;[67] antihistaminic drugs for hay fever[68] and for various allergic diseases;[24,69-71] cortisone acetate in chronic asthma[72] and status asthmaticus;[73] steroids[74] for hay fever; prednisolone and hyroxyzine[75] in allergic diseases; aerosolized or powder inhalations of steroids for bronchial asthma;[76-78] antianginal agents;[67,79,80] rauwolfia serpentina and phenobarbital for hypertension;[81] manganese for rheumatoid arthritis;[82] amphetamine, morphine, heroin, and pentobarbital for inducing mood changes in normal, ill and "post-addict" subjects;[83] tranquilizers;[84-86] a psychotropic amine (methylphenidate) in geriatric patients;[87] hypnotics;[88,89] the hypnotic effect of an antihistamine as compared to phenobarbital;[90] preanesthetic medications;[91] oral and parenteral antipruritic agents;[92,92a,93] methoxsalen for sun-tanning;[94,95] oral prophylaxis of poison ivy dermatitis;[96] zinc ethylene bis-dithiocarbamate in tinea capitis;[67] orally administered nasal decongestants;[97] anticholinergic and ataractic agents in functional and organic gastrointestinal disorders;[14,98] the deodorizing capacity of cholorophyll in advanced carcinoma of the head and neck;[99] meproba-

mate and lobeline as deterrents to smoking;[100] and laxative agents.[101,102] Even a surgical procedure, internal mammary artery ligation for angina pectoris, has been evaluated by a double-blind technique;[103] for the control cases, the chest was opened and the internal mammary arteries exposed, but not ligated.

Almost without exception, double-blind studies have included information regarding side-effects. This is a valuable accessory to this type of study. Only an investigator who has employed the method can fully appreciate the incidence and variety of side-effects attributed by the patients to a preparation which is subsequently found to consist of only a little lactose, or a simple flavored syrup. At least two communications deal with studies primarily designed to elucidate side effects, one dealing with the effect of methoxsalen on liver function[104] and the other with withdrawal symptoms from meprobamate.[105] It is important to bear in mind that comparison of the side-effects of two active medications is valid only when they are given in doses of equal therapeutic effect.[106]

The use of the double-blind technique does not relieve the investigator of responsibility for a proper and trustworthy experimental design. It does not add to the sensitivity of the method. Its only effect is to eliminate bias. A poorly conceived experiment, a large percentage of placebo reactors (essentially those subjects who overreact to any new situation), and overenthusiasm on the part of investigators or patients, all militate against a valid conclusion.[107]

Friend[107] states that after a time the "initial feeling of things being different wears off," and the placebo effect then decreases. He recommends that the investigator devote adequate time to the study, that relatively young subjects are preferable, and that the patients be told, "This medicine may help, may make you worse, or may cause no change." He also advises that, regardless of the sequence of drug and placebo administration, both physician and patient should be told initially that the active drug is being given. The dosage is increased to optimal effect, then both are informed that the placebo will be substituted at some future time without their knowledge; the placebo and the drug are subsequently alternated.

Friend[107] indicates that the characteristics of the investigator are of importance and enumerates four types: (1) The man with specialized knowledge in one field, (2) the man interested in therapy *per se*, (3) the internist, and (4) the general practitioner, busy with many patients, who tends to lack skill in critical evaluation, is influenced by the patient's liking for the drug or treatment situation, and is likely to overread side-effects. Kalz[108] states, "The prejudiced observer appears in two forms—the uncritical enthusiast and the denigrating debunker."

Machella,[109] discussing gastrointestinal studies, believes that experimental subjects should be paid volunteers (although others have pointed out that accepting volunteers introduces a form of selection which may

influence the findings and that such an approach is more suited to human pharmacologic studies rather than therapeutic trials). He also suggests that because of the marked effect of emotions on gastrointestinal function, a superficial evaluation of emotional state should be made just before the experiment.

Moyer[110] differentiates and defines threshold, effective and optimal doses and dose range in drug trials, and emphasizes that overdosage increases the incidence and severity of side-effects. He states that students, residents and other inexperienced observers tend to overread both beneficial and side-effects. He believes that objective evaluation of the effect of tranquilizers on psychoneurotic patients may be achieved by observing rather than questioning them. In discussing the reproducibility of findings, he states that only 37 per cent of psychoneurotics who had responded to a tranquilizer six months previously responded again on readministration.

The method to be used in assessing the effect of the drug must be based on an understanding of pharmacodynamic action and must be sensitive enough to reveal differences, or when more than one dose is used, to discriminate increments in effects.[111] Inclusion in the experimental pattern of an accepted effective drug—a sort of "positive control"—in addition to the unknown and the placebo provides a standard against which the new drug may be compared. Drugs must be administered in adequate, but not toxic, dosage, and continued for a sufficient period of time to reveal therapeutic benefit, if any. Data must be accurately recorded at sufficiently frequent intervals. More subtle difficulties lie in the proper choice of subjects, in total randomization, in maintaining strict controls, and, when indicated, in consideration of various factors not always appreciated in advance as having an influence on the outcome (*e.g.*, barometric pressure, atmospheric temperature, humidity, seasonal influences, et cetera). The seasonal factor is of special import with medications intended for many allergic diseases.[112]

LIMITATIONS AND CRITICISMS

The double-blind technique is neither infallible nor invariably applicable to all drug evaluations. Drugs of obvious or dramatic efficacy and those which manifest a marked pharmacologic action to the subject either do not require or are not suitable for the method. In such situations, coding of the preparations is not an adequate subterfuge (Trouton,[113] Tuteur[114]). One could not conceive of comparing a general anesthetic with a placebo.[111] The method is usually also not suitable with drugs, such as the ganglionic blocking agents, which require strictly individualized dosage.[115] It may not be safe for drugs with which the range between the effective and toxic doses is narrow.

Nevertheless, when drug action is largely subjective, when the measurement of effect may be influenced by the investigator's conscious or sub-

conscious bias, and when unidentified or unidentifiable variables may contribute to the results, the double-blind control goes far to provide objectivity, cancel out extraneous influences, and make possible a more reliable evaluation.

It is probably safe to say that some of the criticism of the double-blind method arises from an expectation of information that the method is not intended and, indeed, cannot be expected, to supply. It cannot conveniently be used to determine the effective dose (although it can compare the relative effectiveness of a series of doses), the toxic dose, the nature of toxic effects, and the full pharmacodynamic actions of a drug. It will not compensate for careless observations, inadequate recording of data, the use of measurements of insufficient sensitivity, the use of inadequate or excessive dosage, or for a poor experimental design. Failure to achieve complete randomization, the selection of non-representative test subjects, unintelligent patients or complicated cases, inadequate frequency of observation, and improperly prepared placebos are other factors which can make double-blind studies misleading. Hence, they are "not free from possible serious errors. . . . Lack of attention to these important details has made a number of so-called 'double-blind studies' recently reported entirely worthless" (DeGraff[116]).

Some critics of the method appear to be alarmed by the apparent "elaborateness" of the experimental pattern, the duration of the trials, the number of subjects required, and the necessity for statistical analysis. Surely, none of these is too great a penalty for the benefits of objectivity and reliability in drug evaluation.

An editorial[117] in this journal about two years ago stated: "There are many of us who have had our doubts as to the value of the double-blind technique for assessing the efficacy of drugs. When the drug effect is easily measurable and the effective and toxic or reactive doses are far apart, there is some validity in the test. . . . But there are experiments in which it is not useful. . . . Only when the dosage schedule and the clinical pharmacology have been established and when, for the individual patient, the maximum dose has been determined, then can conclusions be drawn as to the usefulness of drugs affecting the central nervous, the autonomic and cardiovascular systems.

"Effects due to doses below the level of pharmacologic response, or in excess of those therapeutically effective and of the magnitude which may cause tolerance, should all be considered. . . . The best method of drug evaluation has not yet been evolved, and when it is, for those mentioned and other reasons, the double-blind technique will probably be discarded."

It cannot be denied that thorough pharmacologic study and careful determination of the therapeutic dosage and of levels producing toxic and untoward effects must precede the more elaborate study. If an investigator is foolish enough to attempt a double-blind evaluation employing "doses below the level of pharmacologic response" should we indict the method

or the investigator? Likewise, there is no doubt that the double-blind technique is difficult or even impossible to apply when the dosage of a given drug must be strictly individualized, although even this problem is met in part by the newer methods employing multiple dosage. None of these points invalidates the technique, but merely delimits its usefulness.

This editorial[117] grossly misinterprets a paper by Moyer[115] who says, "After all, it is pointless to study a drug, using a double-blind technique or any other method, if initial screening studies indicate that the drug has little or no therapeutic value within a safe, tolerable dosage range. [Who would argue with this?] Double-blind studies are most useful for evaluating the effect of drugs that are only moderately potent and notably when objective tests of therapeutic efficacy are not available. . . . If the drug is applicable to such an evaluation, double-blind controls can be an effective means of overcoming inexperience, unwarranted enthusiasm, and lack of objectivity in clinical investigation. . . . For these investigators [with limited experience], the double-blind technique was a far superior method of drug study, since it minimized false beneficial effects reported by investigators who are not objective in their approach. . . . If the range between the maximum therapeutic effect and intolerable side-reactions is sufficiently wide, double-blind procedures may be the method of choice for evaluating therapeutic efficacy of drugs used for specific disease entities." Certainly these observations, even if accompanied by some limiting and qualifying statements, do not constitute an attack on the technique.

It has been said that the numerous variables affecting the trial of a drug are often ignored because their importance is not appreciated and their control seems too formidable.[81] The present authors feel that the appreciation of the problem is a matter of physician education, the principles involved having been amply set forth in numerous articles, many of them cited herein. The difficulties of control are not minimized, but rather the advantages are emphasized.

It has been proposed that an institute be created in Denmark for the double-blind testing of the more than seventy new drugs put on the market each year in that country.[118] If this might prove expensive, "the saving afforded by the discarding of remedies found to be valueless might also be great."

The problem of the placebo-reactors, those who cannot discriminate between active and inert drugs, is a constantly recurring theme in drug trials. Inclusion of a large number of such reactors in a study, even with a "cross-over" technique in which the same group of patients takes all the tested preparations, including the placebo, at different times may, unless proper statistical computations are made, give misleading results both as to the efficacy of the drug and an estimation of its optimal dosage.[119] There are, however, as already indicated, methods of recognizing placebo-reactors and making appropriate allowances for their influence on the

results. If "this promises to be no easy task,"[119] it is still not impossible. It must be granted that meeting the necessary conditions for the evaluation of subjective responses to drugs is "complex and exasperatingly time-consuming," but "tedious as these conditions are, . . . they are *not* more costly than the empirical method and are actually far less so."[106]

Only when placebo-reactors are screened out can drug responses be accurately quantified.[106] The techniques of identifying the placebo-reactor were probably first clearly defined by Beecher et al.,[62] but have been repeatedly described since then. Likewise, only after the influence of the placebo-reactors on the data has been eliminated from the calculations is it possible to determine differential responses to two or more drugs. A complicating feature is that placebo-reactors are not consistent in their response.[55,110,119]

The complexities of the problem are indicated in a series of studies by Lasagna, von Felsinger and Beecher,[48,55,83] who nevertheless remain steadfast in employing the double-blind method. The physician-patient relationship and the inherent psychologic structure of the subjects constitute major factors in all drug trials. While there are no differences in sex or intelligence between placebo-reactors and non-reactors, there are significant differences in attitudes, habits, educational background, and personality structure.[55] Placebo-reactors are a more anxious, self-centered, emotionally labile, dependent, and immature group than are non-reactors, who are more rigid and emotionally controlled. Neither group can be considered normal emotionally.[55] Trouton[113] has criticized these personality assessments as based on inadequate evidence. He also points out that the trials give the subjects an opportunity to learn to discriminate between the placebo and the active preparation. Aside from the learning process, these is an element of secondary suggestibility in accounting for placebo-reactors. The nature of the subject (healthy, chronically ill, drug-addicted) and the situation in which a drug is administered are important determinants.[83] Differential personality dynamics, primarily in terms of the balance of mature, socially oriented controls over impulsive, egocentric emotional types are correlated with the type of drug reaction when drugs of various actions are employed.[48] By permitting each patient to be his own control and by standardizing the conditions of administration, one may cancel out many of these variables. Whitehorn[120] points out that placebo effect is a manifestation of complex and important psychological processes which marshall, reinforce, and fulfill certain important health-promoting factors in therapy. He pleads for more research in the psychodynamics of the placebo and concludes that the placebo affords a means of subjecting to scientific investigation both psychiatric and medical treatment. An adequate pharmacologic description of a drug must, in the light of our present knowledge, include a characterization of the patient's attitudes which determine differences in its effects. Accordingly, evalua-

tion of the "inherent" effects of a drug requires placebo controls in the double-blind technique.

In a masterful discussion of the controlled clinical trial, Lasagna[121] makes statements which have been cited out of context as denigrating the double-blind method. "Let us examine the placebo somewhat more critically . . . . since it and 'double-blind' have reached the status of fetishes in our thinking and literature. The Automatic Aura of Respectability, Infallibility, and Scientific Savoir-faire which they possess for many can be easily shown to be undeserved *in all instances*. . . . It is possible to find examples of clinical trials without double-blind control *of all aspects*, but nevertheless yielding useful data." [Italics ours.] However, the entire article leaves no doubt that Lasagna favors the proper use of the placebo control and the double-blind method. He emphasizes the importance of freedom from systematic errors of allocation or assignment (such as placing the sickest patients in one treatment group), concurrent comparison rather than comparison of a group treated five years ago with one drug with a group treated this year with another, and use of appropriate statistical techniques. He shows that comparing a no treatment with a placebo group clearly delineates the placebo effect. He also says that since most patients want to get better and most investigators want to report successful results, each may be tempted to bias on the conscious or unconscious level. The double-blind method eleminates such errors of assessment. Placebos control the element of suggestion and the naturally occurring or spontaneous changes in the course of disease. It is granted that the perfect placebo sometimes cannot be achieved and that placebos may fail to eliminate "negative" bias.

As the example of a clinical evaluation lacking double-blind control in all aspects, Lasagna[121] cites the British trials of streptomycin therapy for pulmonary tuberculosis. But he points out that even here (1) the data being evaluated were objective and (2) the roentgenograms were read "blind." He emphasizes the fact that other experimental safeguards are essential and that the placebo-control and double-blind technique do not necessarily and of themselves insure proper experimental design. The five basic principles of controlled trials, according to Lasagna, are (1) cooperation of investigators with appropriate skills, (2) randomization, (3) the double-blind test, (4) statistical treatment of data, and (5) caution in the generalization of the conclusions reached.

Kast and Loesch[14] list four factors which lead to erroneous drug evaluations: (1) the investigator's enthusiasm, not influencing his observation, but actually altering the response to the drug on the part of the patient who, in the hope and anticipation of being helped, eagerly adopts the physician's attitudes; (2) depending on the physician's attitude, certain "signals"—mild therapeutic results, "toxic" symptoms, accidental changes in the patient's condition, or psychically-induced vasomotor or digestive changes—are over- or under-interpreted; (3) changes in the patient's

life situations may affect his sense of well-being, and hence his apparent response to treatment; and (4) rarely, a bias in observation on the part of the investigator, usually in favor of the drug.

They list five well-thought-out weaknesses in the double-blindfold test: (1) "Signaling phenomena" and extraneous life situations which may influence the patient's interpretation of drug action are not accounted for. (2) Variation in the physician's personality, especially insecurity in not knowing whether he is administering the active drug, may reflect itself in the physician-patient relationship. (3) Large series and lengthy observation are necessary to minimize errors. (4) Many observers of various personalities are needed to eliminate the effects of specific interaction of attitudes of observers with needs of patients. (5) The double blindfold test is subject to "leaks." A powerful drug or one with side effects may clearly reveal itself.

As an alternative to the double-blind method, Kast and Loesch[14] attempted not to eliminate these variables, but to stabilize them. In the first phase of their study, clinic patients suffering from an anxiety syndrome with gastrointestinal somatization were cared for with solicitude, allowed regular visits of about thirty minutes duration at frequent intervals, and were seen simultaneously by two physicians who were available at all times. During this period a tranquilizer-anticholinergic combination was administered. In the second phase, all conditions remained the same except a placebo was substituted without the patient's knowledge. In the third phase, the patients were casually given the original potent drug but in a tablet of different appearance, and the doctor's attitude was changed to an abrupt one. Visits were less frequent, shorter, the patients were made to wait, and the physicians were available only at the appointed time. In a subsequent experiment,[122] the tablet was not changed, but an impersonal, uninterested, and brusque physician was substituted. Their results indicated that a drug is made more effective by a positive attitude on the part of the physician, less effective by a negative attitude, and that an inactive agent (placebo) can be used effectively to improve physician-patient relationship; but even with a positive attitude on the part of the physician, an inactive agent is less effective than the active agent.

In further work, they showed that the percentage of symptomatic improvement was greatly affected by whether the doctor merely cautioned the patients regarding a side effect (dry mouth, when atropine was added to the therapy) or told that it constituted evidence that the drug was working. The present writers find all this a most intriguing and ingenious approach, but not generally applicable, since it introduces additional and less easily manageable variables into the drug evaluation and elicits no more information than the usual double-blind method.

Cole and Griffith[80] studied the physician-patient relationship during a trial of antianginal agents, and designated as the "rapport period" the

initial interval in the course of therapy during which a psychologic relationship is established. During this period the frequency of anginal pain showed a significant decrease, regardless of the random succession of active drug, placebo, and control periods without medication. They concluded that proper assay of antianginal agents—and this would certainly apply to many other medications—must include measurement against control periods after rapport is established.

That the attitude of the investigator, if sufficiently intense and prolonged, may influence the effects of an active drug, even in a carefully controlled double-blind study, was clearly demonstrated by Shapiro et al.[15] The influence on the doctor-patient relationship resulting from a change from initial enthusiasm to one of non-enthusiasm (for the study, not the drug) significantly affected the degree of blood-pressure reduction in a group of hypertensive patients. The indifference of the resident in direct contact with the patients occurred during the latter part of the study because of his personal problems and the imminence of the abrupt termination of his residency to enter military service. In a later study, Shapiro[43] points out that the influence of variables created by non-pharmacologic forces impinging on the patient and the physician are capable of affecting blood pressure and symptoms in the direction of potentiating, mimicking and occasionally masking pharmacologic activity. Among these variables are hospitalization, the psychologic impact of the medicament and the therapeutic regimen, the feeling of the physician toward both the patient and the drug, and the reaction of the patient to psychodynamic stimuli arising from his past and current life situations.

Objecting to the use of the double-blind test in the evaluation of laxative agents,[102] Tomenius[123] questions the application of statistical methods to data which may not be unambiguous, which require a certain intellectual capacity on the part of the patient, which may be influenced by deceptively good results from placebo therapy, and in which it is difficult to maintain the placebo for an adequate period of time. He states that the sources of error act in only one direction—to reduce or efface the superiority of the medicine over the placebo. Incorrectly applied, the double-blind test may give a misleading illusion of scientific exactitude. Sleisenger's reply[124] points out that all medication involves possible pharmacologic potency, therapeutic suggestion, and "bias." The effect of therapeutic suggestion is minimized, although not entirely eliminated, by the use of an inert placebo; the potency of the test drug is measured against the placebo. Bias is best managed by demanding that the effects of therapy be translated into objective parameters insofar as possible. Moreover, the very admission of potential benefit from the placebo is justification for the double-blind procedure.

In a study of the effect of steroid lotions on inflammatory dermatoses, Schamberg, Askovitz and Greenberg[53] were "startled" to find no significant difference between the effect of the steroid and of the control base. They

attempted to explain this by the possible inclusion of too great a proportion of placebo-reactors, of patients with psychosomatic dermatoses, and of patients with dermatoses unresponsive to steroid therapy, and perhaps by inadequate amounts of lotion in some cases and an "active" placebo. Inadvertant contamination of the placebo-treated site through use of the same hand for application of lotion to both areas may be an additional source of error.[125] The data are currently being reworked to see if this may be a factor. The study points up the importance of details of the experimental design, exclusive of the double-blind aspects.

Perhaps the most serious criticisms have been leveled by Batterman[57,126,127] who claims to have followed the double-blind technique faithfully for eighteen years. Disillusioned with the method, he advocates a return to simple clinical testing. While granting that bias may influence the results, he feels that in large groups of patients this becomes less important. He[127] states: "Clinical testing includes (1) studies designed to demonstrate in man a pharmacologic effect confirmatory of animal experiments, (2) an evaluation of the comparative effectiveness and safety of the new drug when used in place of accepted medications, and (3) investigation to elucidate mechanism of action. Screening of new drugs is concerned with the first two. However, there is disagreement as to which of the two is more important for clinical purposes. Various procedures, elaborate as well as simple, have been devised to test a pharmacological effect in man. Appraisal of drugs advocated for relief of subjective phenomenon apparently has been the most difficult. . . . Whenever a double-blind method has been used to evaluate an effective accepted drug, an unknown drug, and a placebo, it was impossible to distinguish in terms of effectiveness or action the three types of medication under investigation. [Numerous studies cited in this review are not in agreement.] . . . The patient may be a placebo reactor, but the physician cannot take the time to find this out nor take the chance that this is so and must therefore prescribe an effective medication. [This illustrates confusion between the aims of patient treatment and of drug evaluation.] . . . An evaluation of . . . any drug advocated for clinical use should attempt to duplicate as closely as possible the conditions under which it will be eventually used by the general practitioner.

"Clinical testing on this level is not 'evaluation at its worst' . . . but rather the most satisfactory means of determining the status of the medication. . . . Since it duplicates exactly how such medications will be utilized by any physician, the results are readily subject to confirmation. . . . Appraisal of newer medications permits many pitfalls. Enthusiastic claims based on artificial experimental procedure methods with limited variables or restricted clinical conditions are rarely confirmed when tested by the general practitioner."[127]

"Emphasis upon subjectivity of the symptoms and techniques devised in establishing objectivity have led physicians away from the clinical

evaluation of usefulness of such drugs. Invariably something is lost by the evaluation of such drugs by specific techniques."[126] If we interpret this correctly, he prefers non-objective and non-specific techniques.

Because of unsatisfactory analgesic results with salicylamide on double-blind testing, and an observation that this method shows a "leveling off" effect, regardless of the potency of the drug, Batterman and Grossman[57] favor a single blindfold technique, the physician being aware of the medicament. Whether both drug and placebo need be studied in the same patient, assuming the over-all responsiveness to a placebo is known, is, they state, open to dispute. In their experience, the double-blind technique may be of value for short-term experiments, especially in hospitalized or bedridden patients, but prolonged administration, whether in ambulatory or hospitalized subjects, yields confusing and misleading results.

Commenting on one of these articles, Russek[128] says, "It is well known that 'the pill the patient swallows, no matter what its nature, acquires potency as a symbol of faith, wisdom and support.' The method of study employed by Batterman and associates apparently utilized no device to neutralize the elements of suggestion and bias and the factors responsible for spontaneous variations in the severity of the anginal state. . . . The ability of a drug to relieve pain should not blunt the physician's interest in determining whether it is a placebo, sedative, or specific agent." According to Best,[129] Batterman and Grossman's own results indicate that their patients were suggestible, and especially so with regard to what the physician believed. "Viewed in its proper perspective, the article of Batterman and Grossman reemphasizes the need for enlightened experimental design. . . . to eliminate unconscious bias. . . ., particularly that dealing with subjective phenomenon and clinical judgment. The double-blind technique is one of the most important tools of such design. . . . Too many things have been 'proved' by uncritical medical studies, resulting in confusion, consternation, and wasted effort in the 'unproving.'" Salamon[130] points out that the salicylamide was probably employed in inadequate dosage in the trial and that in so doing Batterman and Grossman have not clarified either the analgesic action of the drug or the double-blind method. Margolis[131] adds that they failed to follow their own dictum regarding an independent determination of the incidence of placebo response. "Until such time as a more objective procedure for evaluating subjective response than a double-blind technique (other than statistical evaluation of enormous masses of data) is available, it cannot be assumed that data obtained by a double-blind test is unreliable while data obtained by a notoriously deceptive procedure is reliable. . . . It is surprising . . . to find them saying further that they find a single-blind technique, where the physician is aware of the medicament to be use, gives the most useful data for analysis. As between a single-blind and a double-blind study, the only usefulness of data could be to determine the influence of the physician on the results, when he is aware of the identity of the drugs

being tested. . . . Their proposed substitution of a single-blind comparison with a placebo or, as in the case of their salicylamide study, of an uncontrolled test with a small group of patients cannot be regarded as worthy of consideration. . . . Certainly a procedure in which even such things as the tone or the facial expression of the investigator, let alone unintentional or undisguised skepticism or bias, can profoundly influence the results cannot seriously be regarded as superior to the double-blind technique in assaying subjective response."

Tuteur,[114] in a discussion of the pitfalls and fallacies of the double-blind method, points out the difficulty of clearly defining the "target symptoms"— those to be measured in the study—and of properly selecting the patients. These problems are said to be more imposing in the psychiatric field. Moreover, spontaneous remissions are frequently indistinguishable from placebo reactions. [Actually, the determination of the frequency of such occurrences is one of the major purposes of the placebo control period.] He concludes that the double-blind method may be inaccurate and at times even misleading, and is by no means the only method of drug evaluation. DiPalma[132] states that the method is of value only if there is nothing objective to measure, and if the drug is effective the study is no longer blind since both patient and physician may easily recognize the active drug. These points are effectively countered by Modell,[111] Shapiro,[43] and Lasagna and Meier.[133]

Finally, it has been pointed out[134] that "stringent non-interference is difficult to attain in every day practice, where an intensely personal relationship exists. The contrast is fundamental. One cannot take care of sick people without feeling and imparting a measure of confidence in the result; but it is most difficult to assess a new therapy in the face of one's own expectations." To this we say that a drug trial is not "everyday practice" and, in a sense, is not taking care of the sick people, although sick people are usually involved. The difference, as noted early in this review, is one of basic purpose—the difference between medical practice and clinical investigation. Both ends cannot always be served simultaneously or by the same means.

DISCUSSION

From the material we have presented, the following would appear to be the elementary principles in drug evaluation which are widely accepted today:

1. Accurate assessment of the therapeutic effects of any single modality of therapy is difficult unless the response is rapid and dramatic.

2. Many extraneous factors, some recognizable, others obscure or totally undetectable by any currently available means, influence response to all therapy.

3. With few exceptions, the varying clinical course and the inconsistency of symptoms of disease introduce variables into the trial situation.

4. Patients, unlike experimental animals, have psychologic reactions to the treatment situation which influence the pharmacologic effect of drugs acting on subjective symptoms or on clinical conditions which may be affected by psychologic factors.

5. The physician is influenced in his assessments by conscious and unconscious bias with respect to the patient, the drug, and the experiment.

6. Clinical evaluation of drug efficacy and side effects requires precise methodologic techniques and safeguards differing in many fundamental aspects from the clinical use of drugs in the treatment of disease.

The variables introduced by these considerations render the *post hoc; ergo propter hoc* reasoning of, "I gave the patient the medicine. He is better. Therefore, it is an effective drug" completely fallacious. Even a many-fold repetition of such observations by a single investigator is no more impressive, although the combined experience of several observers, at different times, under varying conditions, in scattered geographic locales, and with different approaches to the problem, will add up to probably significant evidence. (In essence, this is what happens when a drug is placed on the market and finds its level of usefulness.) Nevertheless, uncontrolled trials—"just giving the drug to patients"—are not acceptable as representing an evaluation from which broad-scale generalizations may be made. "A doctor makes the same mistake a thousand times and calls it clinical experience."[116]

If simple clinical trial is inadequate (again we must except those drugs which decisively affect objective parameters, which clearly and obviously change the course of disease and/or symptoms, or which markedly reduce a high mortality rate—all statements applying to only a minority of drugs and diseases), the problem becomes one of elaborating a method of drug evaluation which yields convincing evidence of efficacy, and reliable information concerning the milder types of toxicity. Furthermore, it must be capable of comparing a new drug with another of the same category already in use. For reasons made clear in the foregoing sections, the double-blind method, despite its difficulties and limitations, meets the need, provided a good experimental design is used. Results so obtained carry a conviction and an impartiality impossible to achieve otherwise. It is therefore accepted by competent investigators in a wide variety of fields as far superior to uncontrolled clinical trials.

An illuminating example of the reliability of the data derived from the double-blind test occurred in the experience of one of the writers[135] in evaluating a new antihistaminic drug against a well-established preparation and a placebo, all in syrup form. In a series of ninety-eight allergic patients, no significant differences in therapeutic effect were found between the drugs and the placebo. This was puzzling since a concurrent study[69] of similar nature, employing the same compounds in tablet form and utilizing many of the same cases, yielded clear-cut and statistically validated evidence of discrimination between the active drugs and the placebo.

The explanation soon became clear when subsequent independent chemical analysis and pharmacologic assay of the remaining samples of the syrups revealed that complete deterioration of the active ingredients had occurred during prior storage.

Will the future bring forth superior methods of drug evaluation, replacing the double-blind technique? Certainly, new methods will arise. Investigators in many phases of medicine are searching for methods of measuring objectively those sensations and perceptions which we call symptoms. To the extent that they succeed in discovering objective parameters, the problem of assessing symptomatic response to therapy will be simplified. Even so, controlled techniques of evaluation will be necessary in many situations where multiple factors influence the results. In any event, at the present time, objective methods for estimating the severity of pruritus, headache, pain, stiffness, cramps, cough, depression, and numerous other complaints are either rudimentary or do not exist at all. For the time being, therefore, the double-blind method remains secure.

Approaching the problem from a different aspect, we may cite the thoughtful article of Albritton[136] concerning the logic of the design of experiments and the evaluation of experimental data. He sets forth principles required for the prevention (or at least the reduction) of errors and for obtaining comparable data. Correct experimental design requires six unities—unity of time, place, material, procedure, personnel, and mental attitude. Application of these tenets of the experimental method leads one logically to the double-blind technique. For example, the procedure of random selection provides unity of time, place and material, the three being obviously related.

In the last two decades, there has been growing interest in sequential analysis (the sequential probability ratio test). While this has the advantages of a quicker positive or negative answer (although only at a predetermined confidence limit) and of usually requiring a smaller trial sample, it has disadvantages which have been outlined by Lasagna and Meier.[133] Chief among these is the inability to determine to what degree an unknown drug is superior or inferior to its comparable standard.

One other aspect of clinical trials, although alluded to earlier in passing, requires emphasis. Clinical investigations may have one of two fundamentally different goals: (1) to determine the value of a drug in a particular disease, that is, a therapeutic evaluation, or (2) to define the action of a drug in man, that is, a pharmacologic investigation.[111] The results of one type cannot always be applied to the other. Clear definition of the aim of a study will determine to a great extent the choice of trial subjects and the methodology to be pursued, as well as limiting the breadth of generalization to be inferred from the data. Our primary interest in this review is in the therapeutic aspects.

The ethics of the use of placebos, of the double-blind method, and of

experimentation on human beings have been discussed by Lasagna,[121] Albritton,[136] Leslie,[137] Bean[138] and Tuteur,[114] among others. Properly performed, such investigations should not be deleterious to the best interests of the patients and yet may yield data of value. The voluntary consent of the subject is mandatory. He should be informed regarding the nature, duration, purpose and potential hazards of the experiment. Leslie[137] points out that the deception inherent in the use of a placebo is not deceit, the difference lying in intent. Occasionally, ethics (or practical considerations) will interfere with strict adherence to rigid controls or pre-determined experimental design. The welfare of the patient must always be the prime consideration.

Like all strict scientific methodology, this subject lends itself to satirization. We are indebted for the following to an anonymous contributor[139] to a pharmaceutical periodical:

"The value of the double-blind study was first illustrated by studies of the LD-50 of cyanide. In earlier experiments it was considered satisfactory to give, and not to give, the drug to alternate subjects. But now control subjects are given a placebo of exactly the same size, shape and color as the cyanide tablet. By doing the experiments in this way, the clinical impression that cyanide is lethal is verified by observations uncluttered by bias.

"The accuracy of the double-blind test permits evaluation of a drug with far fewer subjects than heretofore; in fact, in some studies it has been possible to reduce the number of subjects to zero. . . .

"Applying the randomization principle to experimental medicine has led to the triple-blind test: The subject doesn't know what he is getting, the nurse doesn't know what she is giving and the investigator doesn't know what he is doing. Half way through the experiment, randomization is increased by a process known as turnabout—the patient administers the drug to the investigator, and the results are evaluated by a student nurse. The famous mathematician, Lewis Carroll, may have had the randomization principle in mind in the phenomenon he described as Jabberwocky or 'unknowable actors executing unknowable actions.' "

In a more serious vein, it must be pointed out that the double-blind method of investigation should be of special interest and value to the allergist. To a considerable extent, his impressions of the clinical course of any patient and the effects of therapy are based on the individual's statements. Periodic physical examinations, to be sure, supplement the subjective opinions, but have their own limitations and, in any event, apply to only a limited period of time. Quantitation of the caliber of nasal or bronchial airways, amount of allergic exudates, mucosal thickness, degree of capillary permeability, extent of smooth-muscle spasm, and—with all due respect to the pulmonary physiologists— pulmonary ventilatory function remain, and seem likely to abide for some time, in the province of the investigative laboratory. Even here, despite many

methods useful in acute experiments, practical considerations make difficult sufficiently frequent re-assessment of drug effects such as would be required because of the daily or hourly variations in the severity of the manifestations of allergic diseases. Accordingly, reliable and trustworthy clinical appraisal of many of the drugs used for the treatment of allergic diseases can best be accomplished by the double-blind method of evaluation.

The increasing use of placebo-controls has been termed "one of the most encouraging signs of the times."[140] In closing, we may quote Modell and Houde:[111] "It is our categorical stand that, in addition to the use of the placebo control, the double-blind control should also be used whenever and wherever it is feasible. We conceive of no disadvantage in the application of the double-blind control—only protection against spurious data." We add that the double-blind method is not a "sacred cow," is not infallible, and will not compensate for any of a number of deficiencies of observation or experimental design. Nonetheless, it provides elements of reliability and impartiality, controls many forms of bias, and properly employed, yields information worthy of credence.

SUMMARY AND CONCLUSIONS

The problem of clinical drug evaluation, and the place of the double-blind method in such evaluation is critically reviewed. The applicability, advantages, and limitations of the double-blind method are discussed. It is concluded that, with proper experimental design, this method is essential for obtaining reliable data in assessing the effects of many drugs.

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818 Medical Arts Bldg. (Dr. Gottlieb)

ERRATUM

On Page 10 of the January, 1960 issue of the ANNALS OF ALLERGY, an unfortunate typographical error occurred, in that the name of Dr. William C. Grater appeared as "Gratex." If the reader will correct the issue in question by hand at this time, the error will not perpetuate itself.

Papers of Interest

Beutler, E.: The hemolytic effect of primaquine and related compounds: a review. Blood 14:103 (Feb.) 1959.
Best review so far published! Absence of glucose 6-dehydrogenase responsible for this and other "allergic reactions" marked by absence of incubation period. New, wide open field for trained allergists.

Halliday, R.: The effect of steroid hormones on the absorption of antibody by the young rat. J. Endocrinol. 18:56 (Jan.) 1959.
Rates of absorption of antibody from guts of rats and mice are associated with duodenal alkaline phosphatase activity, which itself is influenced by cortisone and desoxycorticosterone acetate.

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To be withheld in the young, the old, the debilitated.

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Judicious and up-to-date review.

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The most thorough and detailed study available on the subject. The antigenically active material is non-dialysable and not of carbohydrate nature. It is associated with protein and a yellow pigment.

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Immune-Adherence has been described as a specific immunological reaction wherein micro-organisms or other particulate antigens sensitized with antibody and complement become attached to the surface of human or monkey erythrocytes. The available data indicate that the bond is not electrostatic although attachment due to an electrostatic bond can occur. The studies indicate an immunological reaction based on a complex mechanism, the nature of which still remains obscure.

Gordon, Dan. M., New York, New York. Adrenocortical Steroid Therapy in Ophthalmology. N. Carolina Med. J. 19:473-478 (Nov.) 1958.
A detailed discussion of the present day knowledge of cortical steroid hormones in the treatment of non-allergic disorders.

McLeod, Mary Margaret, Stanford, North Carolina, The Pediatrician and Preventive Allergy. N. Carolina Med. J., 19:93-96 (Mar.) 1958.
Text stresses basic concept, "once allergic, always allergic" and discusses congenital factors, environmental control and medical and surgical precautions.

Fabricant, Noah D.: Progress of Medical Science—Otorhinolaryngology, Am. J. of Med Sciences, 237:499-509, (April) 1959.
A discussion of medical-legal otolaryngology by an expert in the field.

Prickman, L. E., Catastrophic Drug Reactions, U. S. Armed Forces Med. J. 10:333 (Mar.) 1959.
What every physician should have on hand and know how to use, and with dispatch!

Bliss, J. Q. and Walker, J. D., Histamine release by homologous plasma in the Dog. Can. J. Biochem. & Physiol. 37:371 (Mar.) 1959.
In dogs first injection of homologous plasma releases histamine.

Grace, William J.: Thrombocytopenia in a patient taking chlorpropamide. New England J. Med. 260:711-712 (April 2) 1959.
Five days after the first dose of Chlorpropamide, the patient developed a rash which 9 days later became generalized and purpuric. The platelet depression had returned to normal as the rash disappeared following discontinuation of the drug.

Culver, James O.: Respiratory viruses of clinical importance. Kaiser Foundation Med. Bulletin, 7:5-35 (Jan.-Feb.) 1959.
A detailed and excellent review which should be required reading.

Boucot, Katharine R., Horie, Utako and Sokoloff, Martin J. Philadelphia: Survival in lung cancer. New England J. Med. 260:742-746 (April 9) 1959.
A study of 250 consecutive proven cases of primary bronchogenic carcinoma showed the 5 year survival rate as dated from the first film showing any abnormality to be 17 per cent. A plea is made for semi-annual X-ray examinations of the lungs of asymptomatic older patients.

Lobitz, Walter C. Jr., and Jillson, Otis Field: Anecdotes of an agnostic allergist. Arch. Dermat. 78:458-474 (Oct.) 1958.
An amusing but profound discussion of a number of facets of the problem of atopic dermatitis with some interesting observations of the use of intracutaneous tests as clues to its cause.

Mendez, F. L. Jr., and Maurer, Elmer R. A new look at emphysema. Ohio State Med. J. 55:337-343 (March) 1959.
The authors strongly recommend that treatment of pulmonary emphysema consist of prophylaxis and active treatment including chest exercises, antibiotic agents (used systemically and by aerosol) expectorant and antihistaminic medications and bronchoscopy, when warranted. Pulmonary function and pulmonary artery studies are indicated and in selected cases, vagotomy bilateral and complete is recommended.

McCall, W., Jr., and Pool, B. B.: Chemicophysiologic changes of asthmatic secretions leading to atelectasis. North Carolina Med. J. 20:111-113 (March) 1959.
Suggests that the genetic background of an allergic patient suffering from bronchial asthma cause him not only to have increased pulmonary secretions due to cellular injury, but that the secretions themselves are abnormal.

Stanfield, J. B.: A review of cow's milk allergy in infancy, review article. Acta Paediatrica, 48:85-99 (Jan.) 1959 (In English).
As good a review of allergy to cow's milk in infancy as will be seen in a long time.

Christy, N. P., Wallace, E. Z., Gordon, W. E. L. and Jailer, J. W.: On the rate of hydrocortisone clearance from plasma in pregnant women in patients with Laennec's cirrhosis.: J. Clin. Invest. 38:299 (Feb.) 1959.
It is suggested that during pregnancy, tremor homeostasis affects the hydrocortisone-adreno-corticotropin balance so that each can effect the amount released of the other.

News Items

CONNECTICUT STATE MEDICAL SOCIETY SECTION ON ALLERGY

At a recent meeting of the Connecticut State Medical Society Section on Allergy in New Haven, the following officers were elected for 1960:

President.....R. Edward Vioni, M. D., Bridgeport
Vice President.....Irving H. Krall, M. D., Hartford
Secretary.....Marvin Mogil, M. D., New Haven

THE ISRAEL SOCIETY OF ALLERGOLOGY

At the meeting of the Israel Society of Allergology held in Jerusalem on September 16, 1959, the following officers were elected for 1959-61:

President.....M. J. Gutman, M.D., F.A.C.A., Jerusalem
Secretary.....I. Glazer, M.D., Tel Aviv
Treasurer.....N. Lass, M.D., Tel Aviv

Members of the Executive Committee are: A. Liebeskind, M.D., Haifa; Prof. G. Witenberg, Jerusalem; A. Kessler, M.D., Tel Aviv; Z. Kantor, M.D., Tel Aviv.

SYMPOSIUM

Dr. Paul F. McAlenney, Chief of Pediatrics, has announced that a symposium on "The Allergic Child" will be held on April 6, 1960, at the Hospital of St. Raphael, New Haven, Connecticut. The panelists are:

Dr. Susan Dees, Duke University Medical Center
Dr. Jerome Glaser, Rochester School of Medicine
Dr. Douglas Johnstone, Rochester School of Medicine
Dr. Sam Levin, Wayne State University Medical School
Dr. E. S. O'Keefe, Massachusetts General Hospital
Dr. Murray Peshkin, Albert Einstein College of Medicine
Dr. Howard Rapaport, Albert Einstein College of Medicine
Dr. Fred A. Speer, University of Kansas School of Medicine

Guest speaker will be Dr. Bela Schick of Mt. Sinai Hospital, New York, New York.

SOUTHWEST ALLERGY FORUM

The meeting of the Southwest Allergy Forum will be held on April 2-5, 1960, in Oklahoma City, at the Skirvin Hotel. An interesting program is planned and all allergists in the area are invited to attend.

THE AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE

Recently a new society was formed which is to be known as the American Association for the Study of Headache. The purpose behind this organization is to bring together men who are interested in the study of headache, and to allow them to discuss and express their viewpoints on current trends in this field. At the present time, it is planned to have one formal meeting before the annual meeting of the American Medical Association. An informal meeting was held during the Southern Medical Association meeting in Atlanta. Officers include: President, Henry D. Ogden, M.D., 560 S. Galvez, New Orleans, La.; Vice President, Walter C. Alvarez, M.D., Chicago, Ill.; Treasurer, Robert E. Ryan, M.D., St. Louis, Mo.; Secretary, Bayard T. Horton, M.D., Rochester, Minn.; Moderator Martin Tunis, M.D., Montreal, Quebec, Canada.

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